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Chemical compounds with dual activity, processes for their preparation and pharmaceutical compositions

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**Chemical Compounds with Dual Activity, processes for their preparation and pharmaceutical compositions**

The present invention concerns chemical compounds combining affinity and  
 5 antagonism against the human m<sub>3</sub> muscarinic receptor with activity as selective phosphodiesterase IV (PDE IV) inhibitors, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals.

Chronic obstructive pulmonary disease is characterised by airway  
 10 inflammation and impaired expiratory outflow due to chronic bronchitis and/or emphysema. The primary inflammatory cells associated with COPD are macrophages, CD8+ T-cells and neutrophils.

Parasympathetic cholinergic reflexes are the most potent tonically active regulators of bronchoconstriction and of submucosal gland exocytosis and secretion in  
 15 the airways. Post-junctional m<sub>3</sub> receptors mediate cholinergic bronchoconstriction and glandular secretion in the human airways. Prejunctional m<sub>2</sub> autoreceptors modulate the acetylcholine release whereas m<sub>1</sub> receptors located on parasympathetic ganglia inversely facilitate the parasympathetic nerve activity (Barnes P.J., In: "Lung Biology in Health and Disease: Anticholinergic Agents in the Upper and Lower  
 20 Airways", Vol. 134. Spector S.L. (Ed), (1999), 31-57).

The nasal mucosa of the upper airway is also innervated by parasympathetic nerve fibers, activation of which results in glandular hypersecretion from both goblet cells and submucosal seromucinous glands. Activation of m<sub>1</sub> and m<sub>3</sub> receptors results in secretion from mucous and serous glands. The m<sub>3</sub> receptor subtype, also  
 25 present on blood vessels, may play an additional role in nasal congestion through promoting vasodilatation.

Thereby, M<sub>3</sub> and M<sub>1</sub> muscarinic receptor antagonists are indicated for the treatment of diseases associated with airway narrowing or/and mucus hypersecretion (Morley, J. Parasympatholytics in Asthma. Pulmonary Pharmacology (1994). 7, 159-168).

Anticholinergic bronchodilators, particularly selective muscarinic M<sub>3</sub> antagonists, are currently the preferred choice for management of COPD as they are more effective and have fewer side effects compared to β<sub>2</sub>-adrenoceptor agonists. Bronchodilators improve symptoms but do not address the underlying chronic  
 35 inflammation or the changes in airway structure (Hay D.W.P., Current Opinion in Chemical Biology (2000), 4, 412-419).

Amongst phosphodiesterases, PDE IV is the predominant sub-type in inflammatory cells, including mast cells, eosinophils, T lymphocytes, neutrophils and

macrophages. It is also the dominant sub-type in structural cells such as sensory nerves and epithelial cells (Torphy T.J., Am. J. Resp. Crit. Care Med. (1998), 157, 351-370).

Standard treatment with corticosteroids as anti-inflammatory agents has demonstrated limited efficacy (Culpitt S.V., Maziak W., Loukidis S., Nightingale J.A., Matthews J.L., Barnes P.J., Am. J. Resp. Crit. Care Med. (1999), 160, 1635-9); Keatings V.M., Jatakanon A., Wordsell Y.M., Barnes P.J., Am. J. Resp. Crit. Care Med. (1997), 155, 542-8). Selective PDE IV inhibitors, however, have proved to be very efficient in attenuating the responses of various inflammatory cells through their ability to elevate cyclic AMP levels. They are known to modulate activity, migration and apoptosis of neutrophils by inhibiting the production and release of chemokines, superoxide free radicals, leukotrienes and proteolytic and toxic granular enzymes (Torphy T.J., Am. J. Resp. Crit. Care Med. (1998), 157, 351-370).

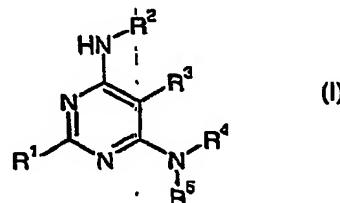
It has now been found that a combination of these two therapeutic activities, bronchodilatation with an M<sub>3</sub> muscarinic antagonist and anti-inflammatory activity with a selective PDE IV inhibitor, in a single compound, provides a new and surprisingly effective approach to the treatment of COPD.

The compounds according to this invention are useful for treating respiratory disorders in connection with Chronic Obstructive Pulmonary Disease (COPD).

Preferred compounds have affinity for the human m<sub>3</sub> muscarinic receptor at concentrations ranging from 100 nM to almost 1 nM and incorporate activity as selective phosphodiesterase IV (PDE IV) inhibitors at concentrations ranging from 2.5 μM to almost 50 nM. These compounds also recognize the m<sub>1</sub>, m<sub>2</sub>, m<sub>4</sub> and m<sub>5</sub> receptors with variable receptor subtype selectivity.

Preferred compounds have been proven to antagonise carbachol-induced contraction of guinea-pig trachea in vitro.

In one aspect, the invention therefore provide compounds having the formula I, or a pharmaceutically acceptable salt thereof,



30

wherein

R<sup>1</sup> is alkyl or cycloalkyl.

R<sup>2</sup> is cycloalkyl.

R<sup>3</sup> is hydrogen, alkyl, halogen, hydroxy, alkoxy or amino,

or  $R^2R^3$  is an alkylene bridging group.

$R^4$  is hydrogen or alkyl.

$R^5$  is cycloalkyl, arylalkyl or heterocycle-alkyl,

or  $NR^4R^5$  is a heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom,

with the proviso that when  $R^2R^3$  is an alkylene bridging group,  $R^1$  is a cycloalkyl.

10 The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms; preferably 1-6 carbon atoms for non-cyclic alkyl and 3-8 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise specified, "lower alkyl").

15 Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, iso- or tert-butyl, and 2,2,2-trimethylethyl.

The term "cycloalkyl", as used herein, refers to a monovalent group of 3 to 18 carbons derived from a saturated cyclic or polycyclic hydrocarbon such as adamantlyl. It may be substituted or unsubstituted. Non-limiting examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[3.2.1]octyl or adamantlyl.

When present as bridging groups, alkyl represents straight or branched chains, C1-12-, preferably C1-4-alkylene.

25 Groups where branched derivatives are conventionally qualified by prefixes such as "n", "sec", "iso" and the like (e.g. "n-propyl", "sec-butyl") are in the n-form unless otherwise stated.

The term "halogen", as used herein, includes an atom of Cl, Br, F, I.

The term "hydroxy", as used herein, represents a group of the formula -OH.

The term "amino", as used herein, represents a group of the formula -NH<sub>2</sub>.

30 The term "thiol", as used herein, represents a group of the formula -SH.

The term "cyano", as used herein, represents a group of the formula -CN.

The term "nitro", as used herein, represents a group of the formula -NO<sub>2</sub>.

35 The term "alkoxy", as used herein, is defined as including -O-R<sup>6</sup> groups wherein R<sup>6</sup> represents an alkyl or a cycloalkyl group. Non-limiting examples are methoxy and ethoxy.

The term "arylalkyl", as used herein, represents a group of the formula -R<sup>7</sup>-aryl in which R<sup>7</sup> is C1-12- straight or branched alkylene. Non-limiting examples are

benzyl, halobenzyl, cyanobenzyl, methoxybenzyl, nitrobenzyl, 2-phenylethyl, diphenylmethyl, (4-methoxyphenyl)diphenylmethyl, indenyl, anthracenylmethyl.

The term "aryl" as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of 1-3 rings and containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl. Aryl radicals are preferably monocyclic containing 6-10 carbon atoms.

Preferred aryl groups are phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, nitro, amino, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl and C1-6-haloalkyl.

The term "alkylthio", as used herein, is defined as including -S-R<sup>6</sup> groups wherein R<sup>6</sup> represents an alkyl or a cycloalkyl group. Non-limiting examples are methylthio, ethylthio, propylthio and butylthio.

The term "heterocycle", as used herein is defined as including an aromatic or non aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. Non-limiting examples of aromatic heterocycles are pyridyl, furyl, pyrrolyl, thienyl, 15 isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinolizinyl, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indolizinyl, purinyl, isoindolyl, carbazolyl, thiazolyl, 1,2,4-thiadiazolyl, thieno(2,3-b)furan, furopyran, benzofuranyl, benzoxepinyl, iso oxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or 20 benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, isochromanyl, indolinyl, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl optionally substituted by alkyl or as described above for the alkyl groups. Non-limiting examples of non 25 aromatic heterocycles are tetrahydrofuran, tetrahydropyran, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro(4.5)dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, 8-thia bicyclo[3.2.1]octanyl, 1,4-dithiepanyl, tetrahydro-2H-thiopyran, azepanyl, azocanyl, or the same which can optionally be substituted with any suitable group; including but not limited to one or more moieties 30 selected from lower alkyl, or other groups as described above for the alkyl groups. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring or where a monocyclic 35

heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo(2.2.1)heptanyl, 7-oxabicyclo(2.2.1)heptanyl, 8-azabicyclo(3.2.1)octanyl.

The term "heterocycle-alkyl", as used herein, represents a group of the formula -R<sup>7</sup>-heterocycle in which R<sup>7</sup> is C1-12- straight or branched alkylene. Non-limiting examples are thiophenemethyl, thiophenethyl, pyridymethyl and pyridylethyl.

The term "pharmaceutically acceptable salt" according to the invention includes therapeutically active, non-toxic base and acid salt forms which the compounds of formula I are able to form.

The acid addition salt form of a compound of formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like.

The compounds of formula I containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

Some of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration. said R and S notation is used in correspondance with the rules described in Pure Appl. Chem., 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers). Reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

Some of the compounds of formula I may also exist in tautomeric forms. Such forms although not explicitly indicated in the above formula, are intended to be included within the scope of the present invention.

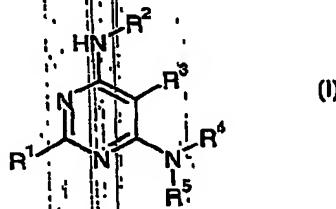
5 The invention also includes within its scope pro-drug forms of the compounds of formula I and its various sub-scopes and sub-groups.

The term "prodrug" as used herein includes compound forms which are rapidly transformed in vivo to the parent compound according to the invention, for example, by hydrolysis in blood. Prodrugs are compounds bearing groups which are removed by 10 biotransformation prior to exhibiting their pharmacological action. Such groups include moieties which are readily cleaved in vivo from the compound bearing it, which compound after cleavage remains or becomes pharmacologically active.

Metabolically cleavable groups form a class of groups well known to practitioners of the art. They include, but are not limited to such groups as alkanoyl (i.e. acetyl,

15 propionyl, butyryl, and the like), unsubstituted and substituted carbocyclic aryl (such as benzoyl, substituted benzoyl and 1- and 2-naphthoyl), alkoxy carbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), phosphate, sulfate, sulfonate, 20 sulfonyl, sulfinyl and the like. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery System", Vol. 14 of the A.C.S. Symposium Series; "Bioreversible Carriers in Drug Design", ed. Edward B. Roche, American 25 Pharmaceutical Association and Pergamon Press, 1987.

Preferred compounds according to the invention are compounds of formula I



or a pharmaceutically acceptable salt thereof wherein

30  $R^1$  is alkyl or C3-7-cycloalkyl,

$R^2$  is C3-7-cycloalkyl,

$R^3$  is hydrogen, C1-4-alkyl, halogen, hydroxy, alkoxy or amino,

or  $R^2R^3$  is a C2-4 alkylene bridging group.

$R^4$  is hydrogen or alkyl,

R<sup>5</sup> is C3-7-cycloalkyl, arylalkyl or heterocycle-alkyl,

or NR<sup>4</sup>R<sup>5</sup> is a heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom,

5 with the proviso that when R<sup>2</sup>R<sup>3</sup> is an alkylene bridging group, R<sup>1</sup> is a cycloalkyl.

Combinations of one or more of these preferred compound groups are especially preferred.

10

Preferably, R<sup>1</sup> is C3-4 alkyl or C3-4 cycloalkyl, more preferably R<sup>1</sup> is selected from the group of cyclopropyl, isopropyl, cyclobutyl, cyclopentyl, 2-methyl-cyclopropyl and cyclopropylmethyl.

15

Preferably, R<sup>2</sup> is C3-4 cycloalkyl, more preferably R<sup>2</sup> is selected from cyclopropyl or cyclobutyl.

Preferably, R<sup>3</sup> is hydrogen, methyl, ethyl, a Cl atom, a F atom, a Br atom, amino or methoxy.

20

In preferred embodiments R<sup>2</sup>R<sup>3</sup> is an alkylene bridging group selected from ethylene, propylene and butylene.

25

Preferably, R<sup>4</sup> is hydrogen or C1-4 alkyl, more preferably R<sup>4</sup> is hydrogen or methyl.

Preferably, R<sup>5</sup> is 2-(2-thienyl)ethyl, 2-furylmethyl, 2-thienylmethyl, 4-pyridinylmethyl, benzyl, 2-(methylsulfonyl)benzyl, 2,6-difluorobenzyl, 2-fluorobenzyl, 2-nitrobenzyl, 3,5-bis(trifluoromethyl)benzyl, 3,5-difluorobenzyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, or 2,2-diphenylethyl.

35

In other preferred embodiments, NR<sup>4</sup>R<sup>5</sup> is 1,3-thiazolidin-3-yl, 1-azepanyl, 1-azocanyl, 3,5-dimethyl-1-piperidinyl, 4-(2-methoxyphenyl)-1-piperidinyl, 4-(hydroxy(diphenyl)methyl)-1-piperidinyl, 4-(trifluoromethyl)-1-piperidinyl, 4,4-difluoro-1-piperidinyl, 4,4-dimethyl-1-piperidinyl, 4-amido-1-piperidinyl, 4-benzyl-1-piperidinyl, 4-carboxy-1-piperidinyl, 4-cyano-4-phenyl-1-piperidinyl, 4-ethoxycarbonyl-1-piperidinyl, 4-ethyl-1-piperidinyl, 4-ethyl-4-methyl-1-piperidinyl, 4-

hydroxy-1-piperidinyl, 4-hydroxy-4-phenyl-1-piperidinyl, 4-hydroxymethyl-1-piperidinyl, 4-methyl-1-piperidinyl, 4-methylene-1-piperidinyl, 4-one-1-piperidinyl, 3,6-dihydro-1(2H)-pyridinyl, 3-azabicyclo[3.2.1]oct-8-yl, 4-pyridinylmethyl, 4-thiomorpholinyl, 2-one-1-azepanyl, 3,4-dihydro-2(1H)-isoquinoliny, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl, 1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl, octahydro-2(1H)-isoquinolinyl or 8-azaspiro[4.5]dec-8-yl.

Most preferred compounds are:

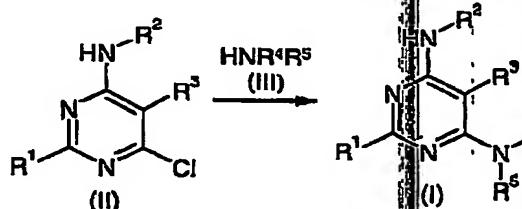
6-(1-azepanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N-[6-(1-azepanyl)-5-chloro-2-cyclopropyl-4-pyrimidinyl]-N-cyclopropylamine; 6-azepan-1-yl-5-bromo-N,2-dicyclopropylpyrimidin-4-amine; 6-(1-azepanyl)-N,2-dicyclopropyl-4-pyrimidinamine; 6-(1-azepanyl)-N<sup>4</sup>,2-dicyclopropyl-4,5-pyrimidinediamine; 6-azepan-1-yl-N-cyclopropyl-2-isopropyl-5-methylpyrimidin-4-amine; 6-(1-azepanyl)-N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-4-pyrimidinamine; 6-(1-azocanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-[4-(trifluoromethyl)piperidin-1-yl]pyrimidin-4-amine; N,2-dicyclopropyl-6-(4,4-difluoro-1-piperidinyl)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-6-(4,4-dimethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-6-(4-ethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-ethyl-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine; N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-methylene-1-piperidinyl)-4-pyrimidinamine; N,2-dicyclopropyl-6-(3,6-dihydro-1(2H)-pyridinyl)-5-methyl-4-pyrimidinamine; 6-(3-azabicyclo[3.2.1]oct-3-yl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-ethyl-6-(4-thiomorpholinyl)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-thiomorpholinyl)-4-pyrimidinamine; N<sup>4</sup>,2-dicyclopropyl-N<sup>6</sup>-(2,6-difluorobenzyl)-5-methyl-4,6-pyrimidinediamine; N<sup>4</sup>-cyclohexyl-N<sup>6</sup>-cyclopropyl-2-(2-methylcyclopropyl)pyrimidine-4,6-diamine; N<sup>4</sup>,2-dicyclopropyl-5-methyl-N<sup>6</sup>-(4-methylcyclohexyl)-4,6-pyrimidinediamine; 6-(1-azepanyl)-N-cyclopentyl-2-cyclopropyl-5-methyl-4-pyrimidinamine; 4-azepan-1-yl-2-cyclopropyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine and 4-azepan-1-yl-2-cyclopropyl-6,7,8,9-tetrahydro-pyrimido[4,5-b]azepine, or pharmaceutically acceptable salts thereof.

The present invention concerns also processes for preparing the compounds of formula I.

The following process description sets forth certain synthesis processes in an illustrative manner. Other alternative and/or analogous methods will be readily apparent to those skilled in this art.

**A.** According to one embodiment, compounds having the general formula I wherein  $R^3 = H$ , alkyl, halogen, alkoxy or hydroxy may be prepared by reaction of a compound of formula II wherein  $R^3 = H$ , alkyl, halogen, alkoxy or hydroxy with an amine of formula III according to the equation:

5



This reaction may be carried out without solvent in the case of high-boiling point amines of formula III or in a high-boiling point alcohol (e.g.: 1-methoxy-2-propanol) as solvent in the case of solid or low boiling point amines of formula III, between 80 and 130 °C.

Compounds of formula III are commercially available or may be prepared under any conventional methods known to the person skilled in the art.

Compounds of formula II wherein  $R^3 = F$ , alkyl, halogen, alkoxy or hydroxy may be prepared by reaction of a compound of formula IV wherein  $R^3 = H$ , alkyl, halogen, alkoxy or hydroxy with a primary amine of formula V according to the equation:

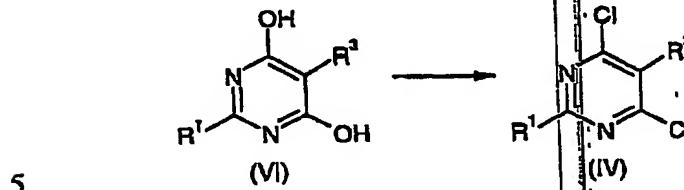
This reaction may be carried out without solvent or in dichloromethane as a solvent, between 30 and 60 °C.

25

Compounds of formula V are commercially available.

10

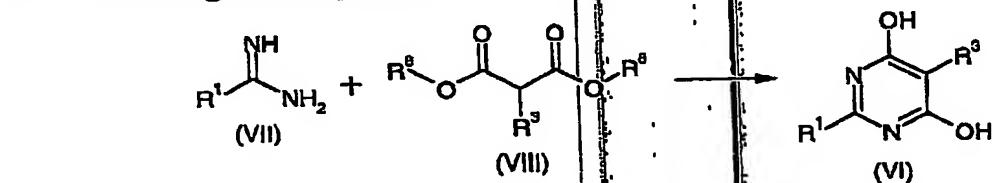
Compounds of formula IV wherein  $R^3 = H$ , alkyl, halogen, alkoxy or hydroxy may be prepared by reaction of a compound of formula VI wherein  $R^3 = H$ , alkyl, halogen, alkoxy or hydroxy with phosphorus oxychloride according to the equation:



10 This reaction may be carried out in boiling phosphorus oxychloride in the presence of one equivalent of N,N-diethylaniline as described in: Evans R.F., Savage G.P., Gough D.A., Aust. J. Chem. (1990), 43, 733-740 or in: Biagi G., Giorgi I., Livi O.,

15 Scartoni V., Lucacchini A., Farmaco (1997), 52, 51-66.

Compounds of formula VI wherein  $R^3 = H$ , alkyl, halogen, alkoxy or hydroxy may be prepared by reaction of a compound of formula VII with a dialkylmalonate of formula VIII wherein  $R^3 = H$ , alkyl, halogen, alkoxy or hydroxy and  $R^8 = Cl-4$ -alkyl according to the equation:



20 This reaction may be carried out in an alcoholic solvent, for example methanol or ethanol, in the presence of 2 equivalents of metallic sodium as a base between 60 and 80 °C as described in: Gershon H., Braun R., Scala A., Rodin R., J. Med. Chem. (1964), 7, 808.

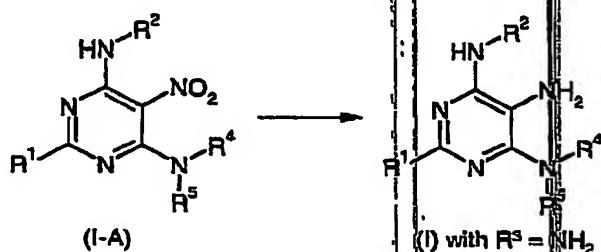
Compounds of formula VIII are commercially available.

25 Compounds of formula VII are commercially available or may be prepared from the corresponding nitrile IX according to the equation:



This reaction may be carried out as described in: Moss R.A., Liu W., Krogh-Jespersen K., Tetrahedron Lett. (1993), 34, 6025-6028.

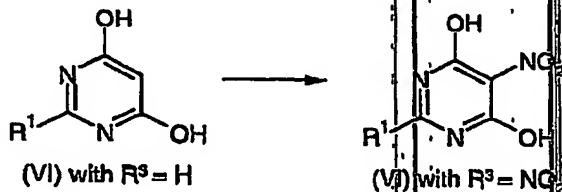
- B. According to another embodiment, compounds having the general formula I  
5 wherein  $R^3 = NH_2$  may be prepared by reduction of the corresponding compound of formula I-A according to the equation:



- 10 This reaction may be carried out by any conventional method known to the person skilled in the art, for example aqueous sodium dithionite in dioxane in the presence of ammonia as described in Chorvat R.J. et al., J. Med. Chem. (1999), 42, 833-848.

- 15 Compounds of formula I-A wherein  $R^3 = NO_2$  may be prepared from a compound VI wherein  $R^3 = NO_2$  following the procedure described in A.

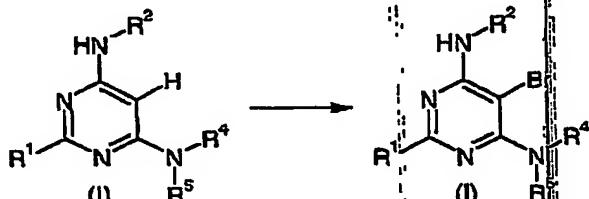
- Compounds of formula VI wherein  $R^3 = NO_2$  may be prepared by reaction of the corresponding compound of formula VI wherein  $R^3 = H$  with nitric acid according to the equation:



- This reaction may be carried out using fuming nitric acid in glacial acetic acid between 30 and 40 °C as described in: Beck J.P. et al., Bioorg. Med. Chem. Lett. (1999), 9, 967 or in: Bagli J. et al., J. Med. Chem. (1988), 31, 814.

C. According to another embodiment, compounds having the general formula I wherein R<sup>3</sup> = Br may be prepared by bromination using N-bromosuccinimide (NBS) of a compound of formula I wherein R<sup>3</sup> = H according to the equation:

5

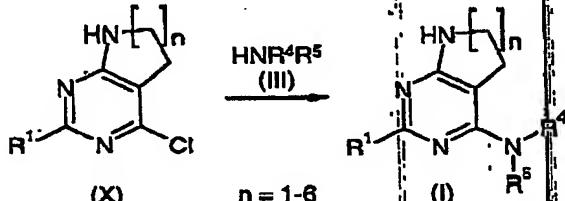


This reaction may be carried out in chloroform as described in: Chen C., Dagnino R., De Souza E.B., Grigoriadis, D.E., Huang C.Q., J. Med. Chem. (1996) 39, 4358-4360.

10

D. According to another embodiment, compounds having the general formula I wherein R<sup>2</sup>R<sup>3</sup> is an alkylene bridging group of formula -(CH<sub>2</sub>)<sub>n</sub>-CH<sub>2</sub>- with n = 1-6 may be prepared by reaction of a compound of formula X wherein n = 1-6 with an amine of formula III according to the equation:

15

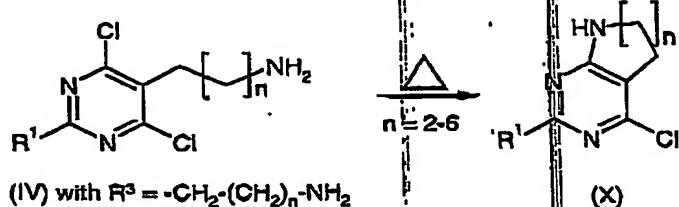


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This reaction may be carried out without solvent in the case of high-boiling point amines of formula III or in a high-boiling point alcohol (e.g.: 1-methoxy-2-propanol) as solvent in the case of solid or low boiling point amines of formula III, between 80 and 130 °C.

D.1 Compounds of formula X wherein n = 2-6 may be prepared by heating a compound of formula IV wherein R<sup>3</sup> represents -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-NH<sub>2</sub> with n = 2-6 according to the equation:

25

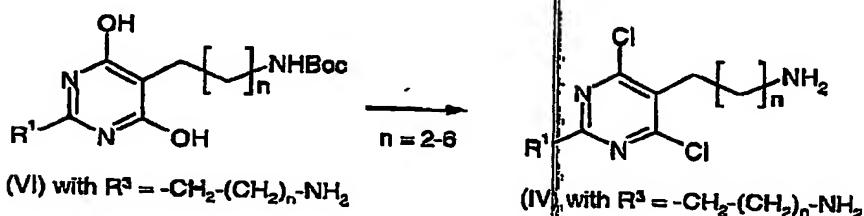


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This reaction may be carried out in a high-boiling point alcohol (e.g.: 1-methoxy-2-propanol) as solvent, between 120 and 140 °C.

5

Compounds of formula IV wherein R<sup>3</sup> represents -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-NH<sub>2</sub>, with n = 2-6, may be prepared by reaction of a compound of formula VI wherein R<sup>3</sup> represents CH<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-NHBOC, with n = 2-6, with phosphorus oxychloride according to the equation:



10

This reaction may be carried out in boiling phosphorus oxychloride in the presence of 1 equivalent of N,N-diethylaniline as described in Evans R.F., Savage G.P., Gough D.A., Aust. J. Chem. (1990), 43, 733-740 or in: Biagi G., Giorgi I., Livi O., Lucacchini A., Farmaco (1997), 52, 61-66.

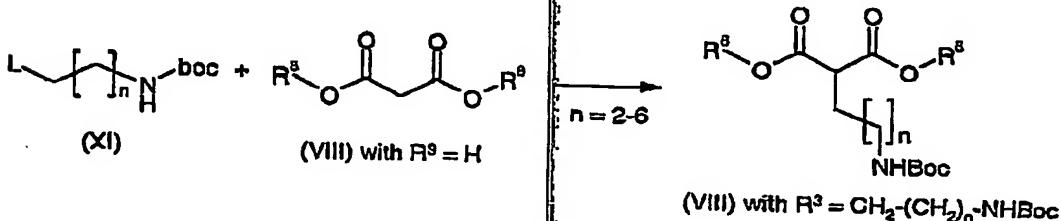
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Compounds of formula VI wherein R<sup>3</sup> represents -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-NHBOC, with n = 2-6, may be prepared by reaction of a compound of formula VII with a dialkylmalonate of formula VIII wherein R<sup>3</sup> represents -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-NHBOC, with n = 2-6, according to the procedure described in A.

20

Compounds of formula VIII wherein R<sup>3</sup> represents -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-NHBOC, with n = 2-6, may be prepared by reaction the corresponding compound of formula VIII wherein R<sup>3</sup> = H with a compound of formula XI wherein L is a leaving group according to the equation:

25



This reaction may be carried out starting from protected alkyl amines bearing a leaving group L (e.g.: halogen, mesylate) in an alcoholic solvent, for example

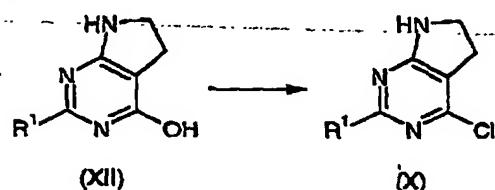
methanol or ethanol, in the presence of 2 equivalents of metallic sodium as a base between 60 and 80 °C.

Compounds of formula VIII are commercially available.

Compounds of formula XI may be prepared by any conventional methods known to the person skilled in the art.

5

D.2 Compounds of formula X wherein n = 1 may be prepared by reaction of a compound of formula XII with phosphorus oxychloride according to the equation:

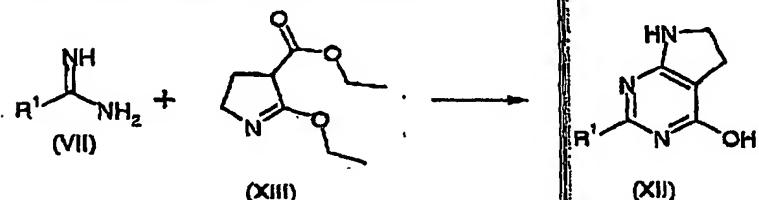


10

This reaction may be carried out in boiling phosphorus oxychloride.

15

Compounds of formula XII may be prepared by reaction of a compound of formula VII with 2-ethoxy-4,5-dihydro-3*H*-pyrrole-3-carboxylic acid ethyl ester (XIII) according to the equation:



20

This reaction may be carried out in an alcoholic solvent, for example methanol or ethanol, in the presence of 1 equivalent of metallic sodium as a base between 60 and 80 °C as described in: Gershon H., Braun R., Scala A., Rodin R., J. Med. Chem. (1964), 7, 808 and in: Granik V.G., Glushkov R.G., Pharm. Chem. J. (Engl. Transl.) (1967), 5, 247-249.

25

2-Ethoxy-4,5-dihydro-3H-pyrrole-3-carboxylic acid ethyl ester of formula (XIII) may be prepared as described in: Granik V.G., Glushkov R.G., Pharm. Chem. J. (Engl. Transl.) (1967), 5, 247-249 and in: Lindstrom K.J., Crooks S.L., Synth. Commun. (1990), 2335-2337.

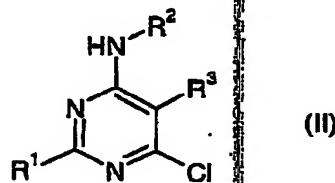
30

When compounds of formula I present one or several stereogenic centres, and that non-stereoselective methods of synthesis are used, resolution of the mixture of

stereoisomers can best be effected in one or several steps, involving generally sequential separation of mixtures of diastereomers into their constituting racemates, using preferably chromatographic separations on achiral or chiral phase in reversed or preferably in direct mode, followed by at least one ultimate step of resolution of each racemate into its enantiomers, using most preferably chromatographic separation on chiral phase in reversed or preferably in direct mode. Alternatively, when partly stereoselective methods of synthesis are used, the ultimate step may be a separation of diastereomers using preferably chromatographic separations on achiral or chiral phase in reversed or preferably in direct mode.

10

In another embodiment, the present invention concerns also the synthesis intermediates of formula II



15

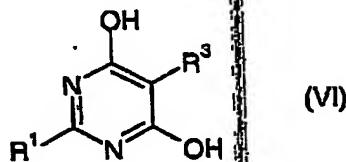
wherein R<sup>1</sup> and R<sup>2</sup> are as defined above and R<sup>3</sup> is hydrogen, alkyl, halogen, alkoxy or hydroxy.

Preferably, the synthesis intermediates of formula II are selected from the group consisting of 6-chloro-N,2-dicyclopropyl-5-fluoro-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine, 5,6-dichloro-N,2-dicyclopropyl-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-5-methoxy-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-5-ethyl-4-pyrimidinamine, N-[6-chloro-2-(2-trans-methylcyclopropyl)-4-pyrimidinyl]-N-cyclopropylamine and its enantiomers, 6-chloro-N-cyclopropyl-5-methyl-2-(2-trans-methylcyclopropyl)-4-pyrimidinamine, 6-chloro-N-cyclopropyl-5-methyl-2-(2-cis-methylcyclopropyl)-4-pyrimidinamine, N-[6-chloro-2-(cyclopropylmethyl)-5-methyl-4-pyrimidinyl]-N-cyclopropylamine, 6-chloro-2-cyclobutyl-N-cyclopropyl-5-methyl-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-5-nitro-4-pyrimidinamine, 6-chloro-N-cyclobutyl-2-cyclopropyl-5-methyl-4-pyrimidinamine, 6-chloro-N-cyclopropyl-2-isopropyl-5-methyl-4-pyrimidinamine and 6-chloro-2-cyclopentyl-N-cyclopropyl-5-methyl-4-pyrimidinamine.

In another embodiment, the present invention concerns the following synthesis intermediate of formula VII: 2-methylcyclopropanecarboximidamide.

35

In another embodiment, the present invention concerns the synthesis intermediates of formula VI



5 wherein R<sup>1</sup> is as defined above and R<sup>3</sup> is alkoxy.

Preferably, the synthesis intermediates of formula VI are selected from the group consisting of: 2-cyclopropyl-5-fluoro-4,6-pyrimidinediol, 5-chloro-2-cyclopropyl-4,6-pyrimidinediol, 2-cyclopropyl-5-methoxy-4,6-pyrimidinediol, 2-cyclopropyl-5-ethyl-4,6-pyrimidinediol, 2-(2-methylcyclopropyl)-4,6-pyrimidinediol, 5-methyl-2-(2-methylcyclopropyl)-4,6-pyrimidinediol, 2-(cyclopropylmethyl)-5-methyl-4,6-pyrimidinediol, 2-cyclobutyl-5-methyl-4,6-pyrimidinediol, 2-cyclopentyl-5-methyl-4,6-pyrimidinediol, [3-(2-cyclopropyl-4,6-dihydroxy-pyrimidin-5-yl)-propyl]-carbamic acid tert-butyl ester, [4-(2-cyclopropyl-4,6-dihydroxy-pyrimidin-5-yl)-butyl]-carbamic acid tert-butyl ester.

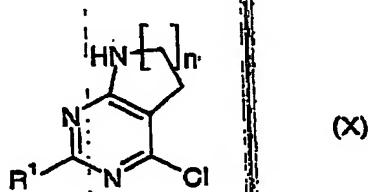
In another embodiment, the present invention concerns the following synthesis intermediates of formula IV: 4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine, 4,5,6-trichloro-2-cyclopropylpyrimidine, 4,6-dichloro-2-cyclopropyl-5-pyrimidinyl methyl ether, 4,6-dichloro-2-cyclopropyl-5-ethylpyrimidine, 4,6-dichloro-2-(2-methylcyclopropyl)pyrimidine, 4,6-dichloro-5-methyl-2-(2-methylcyclopropyl)pyrimidine, 4,6-dichloro-2-(cyclopropylmethyl)-5-methylpyrimidine, 4,6-dichloro-2-cyclobutyl-5-methylpyrimidine, 4,6-dichloro-2-isopropyl-5-methylpyrimidine, 4,6-dichloro-2-cyclopentyl-5-methylpyrimidine.

25

In another embodiment, the present invention concerns the following synthesis intermediate of formula I-A: 6-(1-azepanyl)-N,2-dicyclopropyl-5-nitro-4-pyrimidinamine.

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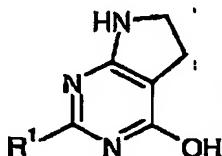
In another embodiment, the present invention concerns the synthesis intermediates of formula X



wherein n is 1-6 and R<sup>1</sup> is as defined above.

Preferably, the synthesis intermediates of formula X are selected from the group consisting of: 4-chloro-2-cyclopropyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine, 4-chloro-2-cyclopropyl-5,6,7,8-tetrahydro-5H-pyrrolo[2,3-d]pyrimidine, and 4-chloro-2-cyclopropyl-6,7,8,9-tetrahydro-5H-pyrimido [4,5-b] azepine.

In another embodiment, the present invention concerns the synthesis intermediates of formula XII



(XII)

10

wherein R<sup>1</sup> is cycloalkyl.

Preferably, the synthesis intermediate of formula XII is 2-cyclopropyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-ol.

15

It has now been found that compounds of formula I and their pharmaceutically acceptable salts are useful in a variety of pharmaceutical indications.

For example, the compounds according to the invention are useful for the treatment of respiratory disorders in connection with the Chronic Obstructive Pulmonary Disease (COPD).

These compounds may also be used for treating symptoms related to disorders such as chronic bronchitis, emphysema, cough, either directly linked to COPD or not, and also cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis and asthma.

25

Preferred compounds have antagonist activity against the human m3 muscarinic receptor at concentrations ranging from 100 nM to almost 1 nM and incorporate activity as selective phosphodiesterase IV (PDE IV) inhibitors at concentrations ranging from 2.5 µM to almost 50 nM. These compounds also recognize the m1, m2, m4 and m5 receptors with variable receptor subtype selectivity.

Preferred compounds have been proven to antagonise carbachol-induced contraction of guinea-pig trachea in vitro.

35

In addition the compounds according to the invention may be used in the treatment of the following symptoms which are related to PDE IV or M<sub>3</sub>:

**PDE IV-related**

Amongst PDEs, PDE IV is highly selective for cAMP. Four human PDE IV subtypes have been identified, with distinct tissue and cellular distribution. PDE IVA appears to be distributed ubiquitously. PDE IVB is expressed in heart, brain, skeletal muscle and lung. PDE IVC is abundant in neuronal tissue but is absent from immune and inflammatory cells. PDE IVD is abundant in immune and inflammatory cells. Functional effects such as those associated with gastric acid secretion, relaxation of the myometrium, bronchorelaxation and diuresis in the kidney have been attributed to the effect of PDE IV inhibition. This argues in favour of the interest of such approach for treating GI disorders, kidney dysfunction, respiratory and inflammatory disorders.

Furthermore, PDE IV may also be of biological significance and therapeutic relevance in CNS therapeutic indications such as depression and dementia. The hypothesis is that enhanced cAMP availability produced by inhibition of PDE IV stimulates the increase in noradrenaline function produced by classical antidepressants such as imipramine at the post-synaptic level (Wachtel H., Pharmacopsychiatry (1990), 23, 27-32). Denbufylline has also been shown to increase cAMP in cortical slices, indicating a potential in the treatment of cognitive impairment (Nicholson C.D., Psychopharmacology (1990), 101, 147-159).

In addition, the PDE IV enzyme may also be a potential target for anticancer therapy, due to its inhibitory effect on tumour cell growth (Drees M., Zimmermann R., Eisenbrand G., Cancer Res. (1993), 53, 3058-3061), and PDE IV inhibition may be beneficial in tissue transplantation (Pinsky D., Oz M., Morris S., J. Clin. Invest. (1993), 92, 2994-3002) and for cardiovascular diseases including atherosclerosis and hypertension (Demouliou-Mason C., Exp. Opin. Ther. Patents (1994), 4, 813-823).

**M<sub>3</sub>-related**

**Lower urinary tract disorders:**

The parasympathetic nervous system is the principal excitatory innervation to the detrusor smooth muscle of the urinary bladder. Acetylcholine, released from postganglionic cholinergic nerves, activates post-junctional muscarinic receptors in the detrusor which causes contraction of the bladder that is coordinated with outlet relaxation and leads to voiding of urine (De Groat W.C., Booth A.M., Yoshimura N., In: "Nervous control of the urogenital system", Maggi, C.A. (Ed), Harwood Academic Publishers, Amsterdam, (1993), 227-290). Both m<sub>2</sub> and m<sub>3</sub> muscarinic receptors are expressed in the smooth muscle of the bladder detrusor (Hegde S.S., Eglen R.M., Life Science (1999), 64, 419-428). Muscarinic m<sub>3</sub> receptors play a key role in mediating the contractile effect of Acetylcholine (ACh) but m<sub>2</sub> receptors may also contribute to

micturition through opposing the relaxing effect of adrenergic sympathetic tone. Prejunctional m1 facilitory muscarinic receptors may also be involved.

Aging, inflammation or irritants and neurological trauma may result in increased nerve afferent and efferent activity and overactive bladder to become a leading cause of trouble presenting some symptoms such as urgency and frequency micturition and incontinence.

Therefore, non-selective muscarinic M<sub>3</sub> antagonists have utility in the treatment of bladder disorders including urge and mixed urinary incontinence, pollakiuria, neurogenic or unstable bladder, hyperreflexia and chronic cystitis (Gillberg P.G., Sundquist S., Nilvebrant L., Eur. J. Pharmacol. (1998), 349, 285-292; Schwantes U., Topfmeler P., International Journal of Clinical Pharmacology and Therapeutics (1999), 37, 209-218; Andersson K.E. et al., In: "Incontinence. 1st International Consultation on Incontinence - June 28 - July 1, 1998 - Monaco", Abrams P., Khouri S., Wein A., Les Editions Vingt et Un, Paris. (1999), 447-486).

15

#### Gastrointestinal disorders:

Contractility of the smooth muscle of the gastrointestinal tract is under the control of parasympathetic tone and Acetylcholine (ACh). Contraction of the intestinal smooth muscle is principally dependent upon activation of muscarinic m3 receptors although stimulation of m2 muscarinic receptors might synergize with m3-mediated responses (Sawyer G.W., Ehlert F.J., J. Pharmacol. Exp. Ther. (1998), 284, 269-277).

Gastric secretion is also under the control of the parasympathetic nervous system. Secretagogue effect of ACh depend on the activation of post-junctional m3 receptors whilst m1 receptors located on the post-ganglionic nerves of the myenteric plexus have a facilitatory role on the parasympathetic nerve activity.

Therefore, m<sub>3</sub> and m<sub>1</sub> muscarinic receptor antagonists are potentially useful for treating gastrointestinal disorders associated with intestinal hypermotility such as irritable bowel syndrome, spastic colitis and diverticulosis (Wallis R.M., Napier C.M., Life Science (1999), 64, 395-401) and to reduce acid secretion, gastric motility, to aid the healing of peptic ulcers and to treat gastroesophageal reflux disease and stress-related erosive syndrome (Rademaker J.W., Hunt R.H., Scand. J. Gastroenterol. (1990), 25, 19-26; Coruzzi G., Adami M., Bertaccini G., Arch. Int. Pharmacodyn. Ther. (1989), 302, 232-241).

35

#### CNS - Cognitive disorders

The release of acetylcholine from central cholinergic nerves is under autoinhibitory control via m2 or m4 autoreceptors.

Therefore, M<sub>2</sub> or M<sub>4</sub> antagonists might reduce the levels of ACh released and may offer a potential approach for the treatment of cognitive disorders causally related

to a deterioration or deficit of cortical cholinergic neurons, such as in senile dementia and Alzheimer's disease (Doods H.N., Quirion R., Mihm G., Life Science (1993), 52, 497-503).

5 CNS - Locomotor disorders

The nigrostriatum has many more m<sub>4</sub> receptors than any other tissue (Santiago M.P., Potter L.T., Brain Res. (2001), 894, 12-20). These receptors exert inhibitory control on Dopamine (D<sub>1</sub>) receptor mediated locomotor stimulation (Gomeza J., Zhang L., Kostenis E., Felder C., Bymaster F., Brodkin J., Shannon H., Xia B., Deng C., Wess J., Proc. Natl. Acad. Sci. USA. (1999), 96, 10483-10488).

10 Therefore, centrally active M<sub>4</sub> muscarinic antagonists may have the potential to treat Parkinsonian's disorders and dyskinesia thought to be causally related to a deterioration of dopaminergic neurons in the nigrostriatum (Salamone J.D., Carlson B.B., Correa M., Wisniecki A., Nisenbaum E., Nisenbaum L., Felder C., In: "Society for Neuroscience 30<sup>th</sup> Annual Meeting New Orleans, Nov 2000", Mayorga et al., (1999), Abstract 278.5; Mayorga A.J., Cousins M.S., Trevitt J.T., Conlan A., Gianutsos G., Salamone J.D., Eur. J. Pharmacol. (1999), 364, 7-11).

15 CNS - feeding disorders

20 Activation of muscarinic m<sub>3</sub> receptors located in the lateral hypothalamus contributes to feeding behaviour (Yamada M. et al., Nature (2001), 410, 207-212).

Thereby, M<sub>3</sub> antagonists may offer new therapeutic perspectives for the treatment of obesity, bulimia and metabolic syndrome.

25 CNS - sleeping disorders

Activation of m<sub>1</sub> and m<sub>3</sub> receptors in the mediodorsal pontine tegmentum results in a marked increased in paradoxical sleep indicating that centrally active M<sub>3</sub> antagonists can be useful for treating sleep disorders (Imeri L., Bianchi S., Angeli P., Mancia M., Brain Res. (1994), 636, 68-72; Sakai K., Onoe H., Eur. J. Neurosci. (1997), 9, 415-23).

30 Cardiovascular disorders

The heart rate is under parasympathetic tone via muscarinic m<sub>2</sub> receptors on the SA node.

35 Therefore, m<sub>2</sub> receptor antagonists are of potential value in the emergency treatment of acute myocardial infarction where the dominant autonomic influence of the heart is via the vagus nerve, causing sinus or nodal bradycardia (Van Zwieten P.A., Doods H.N., Cardiovascular Drugs and Therapy (1995), 9, 159-167).

Thus the present invention concerns a compound of formula I or a pharmaceutically acceptable salt thereof for use as a medicament.

In a further aspect, the present invention concerns the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of PDE IV and/or Mg<sup>2+</sup> related disorders such as mentioned above.

In particular, the present invention concerns the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of COPD or of symptoms related to disorders such as chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis and asthma.

The present invention also concerns a method for treating COPD or symptoms related to disorders such as chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis and asthma in a mammal in need of such treatment, comprising administering at least one compound of formula I or a pharmaceutically acceptable salt thereof to a patient.

The term "treatment" as used herein includes curative treatment and prophylactic treatment. By "curative" treatment is meant efficacy in treating a current symptomatic episode of a disorder or condition. By "prophylactic" treatment is meant prevention of the occurrence or recurrence of a disorder or condition.

For treating diseases, compounds of formula I, or their pharmaceutically acceptable salts, may be employed at an effective daily dosage and administered in the form of a pharmaceutical composition.

25 Therefore, another embodiment of the present invention concerns a pharmaceutical composition comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable diluent or carrier.

To prepare a pharmaceutical composition according to the invention, one or more of the compounds of formula I or a pharmaceutically acceptable salt thereof, is intimately admixed with a pharmaceutical diluent or carrier according to conventional pharmaceutical techniques known to the skilled practitioner.

35 Pharmaceutical compositions comprising compounds according to the invention can, for example, be administered orally or parenterally, i.e., intravenously, intramuscularly, subcutaneously or by inhalation (orally or intranasally). In a preferred embodiment, the pharmaceutical compositions are administered by inhalation.

Pharmaceutical compositions suitable for oral administration can be solids or liquids and can, for example, be in the form of tablets, pills, dragees, gelatin capsules,

solutions, syrups, aerosols, powders for inhalation and the like. Pharmaceutical compositions suitable for administration by inhalation are preferred.

The following examples are provided for illustrative purposes.

5

1 EXAMPLE 1: Analytical characterization of the compounds.

Unless otherwise specified in the examples, characterization of the compounds was performed according to the following methods:

NMR spectra are recorded on a BRUKER AC 250 Fourier Transform NMR Spectrometer fitted with an Aspect 3000 computer and a 5 mm  $^1\text{H}/^{13}\text{C}$  dual probehead or BRUKER DRX 400 FT NMR fitted with a SG Indigo2 computer and a 5 mm inverse geometry  $^1\text{H}/^{13}\text{C}/^{15}\text{N}$  triple probehead. The compound is studied in DMSO-d<sub>6</sub> (or CDCl<sub>3</sub>) solution at a probe temperature of 313 K and at concentrations ranging from 2 to 20 mg/ml. The instrument is locked on the deuterium signal of DMSO-d<sub>6</sub> (or CDCl<sub>3</sub>). Chemical shifts are given in ppm downfield from TMS taken as internal standard.

Mass spectrometric measurements in LC/MS mode are performed as follows:

HPLC conditions

Analyses are performed using a WATERS Alliance HPLC system mounted with an INERTSIL ODS 3-, DP 5  $\mu\text{m}$ , 250 X 4.6 mm column.

The gradient runs from 100 % solvent A (acetonitrile, water, TFA (10/90/0.1. v/v/v)) to 100 % solvent B (acetonitrile, water, TFA (90/10/0.1. v/v/v)) in 7 min with a hold at 100 % B of 4 min. The flow rate is set at 2.5 ml/min and a split of 1/10 is used just before API source. The chromatography is carried out at 30 °C.

25

MS conditions

Samples are dissolved in acetonitrile/water, 70/30, v/v at the concentration of about 250  $\mu\text{g}/\text{ml}$ . API spectra (+ or -) are performed using a FINNIGAN (San Jose, CA, USA) LCQ ion trap mass spectrometer. APCI source operates at 450 °C and the capillary heater at 160 C. ESI source operates at 3.5 kV and the capillary heater at 210 °C.

30

Mass spectrometric measurements in EI/DIP mode are performed as follows: samples are vaporized by heating the probe from 50 °C to 250 °C in 5 min. EI (Electron Impact) spectra are recorded using a FINNIGAN (San Jose, CA, USA) TSQ 700 tandem quadrupole mass spectrometer. The source temperature is set at 150 °C.

35

Specific rotation is recorded on a Perkin Elmer MC241 or MC341 polarimeter. The angle of rotation is recorded at 25 °C on 1 % solutions in MeOH. For some molecules, the solvent is CH<sub>2</sub>Cl<sub>2</sub> or DMSO, due to solubility problems.

Water content is determined using a Metrohm microcoulometric Karl Fischer titrator.

Preparative chromatographic separations are performed on silicagel 60 Merck, particle size 15-40 µm, reference 1.15111.9025, using in-house modified Jobin Yvon-type axial compression columns (80 mm i.d.), flow rates between 70 and 150 ml/min. Amount of silicagel and solvent mixtures are as described in individual procedures.

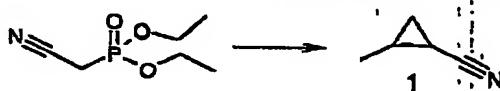
Preparative chiral chromatographic separations are performed on a DAICEL Chiraldpak AD 20 $\mu$ m, 100 $\times$ 500 mm column using an in-house build instrument with various mixtures of lower alcohols and C5 to C8 linear, branched or cyclic alkanes at  $\pm$  350 ml/min. Solvent mixtures are as described in individual procedures.

Melting points are determined on a Büchi 535 or 545 Tottoli-type fusionometre, and are not corrected, or by the onset temperature on a Perkin Elmer DSC 7.

Unless specified otherwise in the examples, the compounds are obtained in the neutral form.

**EXAMPLE 2:** Synthesis of amidines of formula VII

## 2.1 Synthesis of 2-methylcyclopropanecarbonitrile 1



To a suspension of sodium hydride (11 g, 0.28 mol, 60 % in oil, washed two times with n-hexane) in tetrahydrofuran (150 ml) is added diethyl cyanomethylphosphonate (45.5 g, 0.25 mol) over 0.5 h, at room temperature. The mixture is stirred 0.25 h. Propylene oxide (16.3 g, 0.28 mol) is added dropwise at room temperature and the solution is stirred for 1 h then heated at reflux for 4 h. The mixture is cooled and ammonium chloride (115 g) is added. The solvent is distilled, the residue is poured onto crushed ice and extracted three times with diethyl ether. The combined organic layers are washed with brine, dried over magnesium sulfate, concentrated (atmospheric pressure) and the final residue is distilled under reduced pressure (75 °C, 70 mm Hg) to afford pure 2-methylcyclopropanecarbonitrile 1 (7.5 g, 33 %) as an oil.

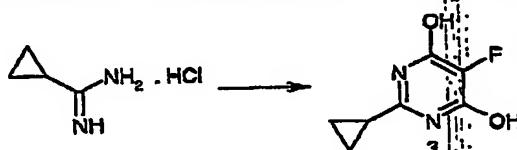
## 2.2 Synthesis of 2-methylcyclopropanecarboximidamide hydrochloride **2**



Gaseous hydrochloric acid is passed through a solution of 2-methylcyclopropanecarbonitrile 1 (7.5 g, 92 mmol) in ethanol (8.5 ml) at 0 °C until 7 g have been absorbed. The resulting mixture is kept in the refrigerator for 48 h. Ethanol (150 ml) is then added and gaseous ammonia is passed through the solution at -5 °C for 4 h. The solvent is evaporated in vacuo. Hydrochloric acid in diethyl ether (8 N solution, 3 ml) is added and the solution is concentrated and dried in vacuo to afford 2-methylcyclopropanecarboximidamide hydrochloride 2 (6.15 g, 50 %) as a paste that is used without further purification.

10 EXAMPLE 3: synthesis of 4,6-pyrimidinediol derivatives of formula VI.

3.1 Synthesis of 2-cyclopropyl-5-fluoro-4,6-pyrimidinediol 3.



15 Sodium (646 mg, 28 mmol) is dissolved in methanol (50 ml) under a nitrogen atmosphere. Cyclopropanecarboximidamide hydrochloride (3.40 g, 28 mmol) is added in one portion. The mixture is stirred at room temperature for 0.25 h, then filtered upon hyflocel. The filtrate is concentrated in vacuo. This free base is added to a solution of sodium (1.29 g, 56 mmol) in methanol (50 ml) under a nitrogen atmosphere, at room temperature. Diethylfluoromalonate (5 g, 28 mmol) is added and the mixture is stirred at 60 °C for 5 h. The solvent is evaporated and the yellowish solid obtained is dissolved in 60 ml of water. The pH is adjusted at 6 with a 5 N HCl solution and the white precipitate formed is filtered and dried. 2-cyclopropyl-5-fluoro-4,6-pyrimidinediol 3 (3.6 g, 76 %) is obtained as a white powder and used in the next step without further purification.

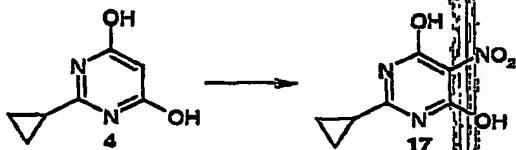
20 25  $^1\text{H}$  NMR (250 MHz, DMSO): 0.95 (m, 4H), 1.83 (m, 1H), 12.1 (bs, 2H).

Compounds described in table 1 can be synthesized in an analogous way.

Table 1

<b>4</b>	2-cyclopropyl-4,6-pyrimidinediol	Patent Geigy 1966, NL6513321
<b>5</b>	2-cyclopropyl-5-methyl-4,6-pyrimidinediol	MS ( $M^+$ ): 166
<b>6</b>	5-chloro-2-cyclopropyl-4,6-pyrimidinediol	MS ( $M^+$ ): 187/189
<b>7</b>	2-cyclopropyl-5-methoxy-4,6-pyrimidinediol	MS ( $M^+$ ): 182
<b>8</b>	2-cyclopropyl-5-ethyl-4,6-pyrimidinediol	MS ( $M^+$ ): 180
<b>9</b>	2-(2-methylcyclopropyl)-4,6-pyrimidinediol	$^1H$ NMR (250 MHz, DMSO): 0.83 (m, 1H), 1.11 (d, 3H), 1.18 (m, 1H), 1.38 (m, 1H), 1.61 (m, 1H), 5.03 (s, 1H)
<b>10</b>	5-methyl-2-(2-methylcyclopropyl)-4,6-pyrimidinediol	MS ( $MH^+$ ): 181
<b>11</b>	2-(cyclopropylmethyl)-5-methyl-4,6-pyrimidinediol	MS ( $MH^+$ ): 181
<b>12</b>	2-cyclobutyl-5-methyl-4,6-pyrimidinediol	MS ( $M^+$ ): 180
<b>13</b>	2-isopropyl-5-methyl-4,6-pyrimidinediol	MS ( $MH^+$ ): 169
<b>14</b>	2-cyclopentyl-5-methyl-4,6-pyrimidinediol	MS ( $M^+$ ): 194
<b>15</b>	[3-(2-cyclopropyl-4,6-dihydroxy-pyrimidin-5-yl)-propyl]-carbamic acid tert-butyl ester	MS ( $MH^+$ ): 310
<b>16</b>	[4-(2-cyclopropyl-4,6-dihydroxy-pyrimidin-5-yl)-butyl]-carbamic acid tert-butyl ester	MS ( $MH^+$ ): 324

### 3.2 Synthesis of 2-cyclopropyl-5-nitro-4,6-pyrimidinediol 17.



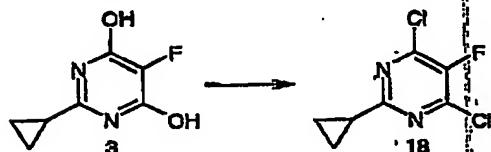
5

Glacial acetic acid (90 ml) is added to fuming nitric acid (40 ml) at 0 °C. The solution is warmed to 30 °C and 2-cyclopropyl-4,6-pyrimidinediol 4 (35 g, 0.25 mol) is added in portions. The temperature is kept between 30 and 40 °C. After 1h, the mixture is poured onto crushed ice and filtered. The filtrate is concentrated to 50 ml in vacuo. Methanol is added and the precipitate is filtered and dried. Pure 2-cyclopropyl-5-nitro-4,6-pyrimidinediol 17 (39.8 g, 81%) is obtained and used in the next step without further purification.

MS ( $M^+$ ): 197.

4 EXAMPLE 4: synthesis of 4,6-dichloropyrimidine derivatives of formula IV.

4.1 Synthesis of 4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine 18:



5 2-cyclopropyl-5-fluoro-4,6-pyrimidinediol 3 (3.51 g, 21 mmol) is suspended in phosphorus oxychloride (15 ml). A mixture of N,N-diethylaniline (3.08 g, 21 mmol) and phosphorus oxychloride (15 ml) is added dropwise to the suspension at 0 °C. The resulting mixture is stirred at 110 °C for 2 h, then cooled to room temperature. The brown solution is poured onto crushed ice and extracted five times with dichloromethane. The combined organic layers are washed three times with a 1 N HCl solution, dried over magnesium sulfate and concentrated in vacuo to afford 4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine 18 as an orange oil (4.80 g, 100 %) which is used in the next step without further purification.

10 MS ( $M^+$ ): 205/207/209.  
15 Compounds described in table 2 can be synthesized in an analogous way.

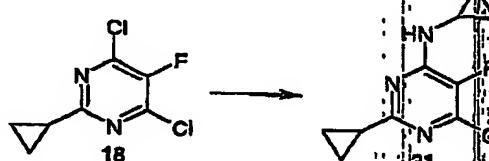
Table 2

<b>19</b>	4,6-dichloro-2-cyclopropylpyrimidine	MS ( $M^+$ ): 189/191/193
<b>20</b>	4,6-dichloro-2-cyclopropyl-5-methylpyrimidine	MS ( $M^+$ ): 202/204/206
<b>21</b>	4,5,6-trichloro-2-cyclopropylpyrimidine	MS ( $M^+$ ): 222/224/226
<b>22</b>	4,6-dichloro-2-cyclopropyl-5-pyrimidinyl methyl ether	MS ( $M^+$ ): 218/220/222
<b>23</b>	4,6-dichloro-2-cyclopropyl-5-ethylpyrimidine	$^1\text{H}$ NMR (250 MHz, $\text{CDCl}_3$ ): 1.12 (m, 4H), 1.20 (t, 3H), 2.16 (m, 1H), 2.85 (q, 2H)
<b>24</b>	4,6-dichloro-2-(2-methylcyclopropyl)pyrimidine	bp. = 85°C/1 mmHg
<b>25</b>	4,6-dichloro-5-methyl-2-(2-methylcyclopropyl)pyrimidine	MS ( $M^+$ ): 216/218/220
<b>26</b>	4,6-dichloro-2-(cyclopropylmethyl)-5-methylpyrimidine	MS ( $MH^+$ ): 217/219/221
<b>27</b>	4,6-dichloro-2-cyclobutyl-5-methylpyrimidine	MS ( $MH^+$ ): 216/218/220
<b>28</b>	4,6-dichloro-2-cyclopropyl-5-nitropyrimidine	MS ( $M^+$ ): 233/235/237
<b>29</b>	4,6-dichloro-2-isopropyl-5-methylpyrimidine	MS ( $M^+$ ): 204/206/208
<b>30</b>	4,6-dichloro-2-cyclopentyl-5-methylpyrimidine	MS ( $M^+$ ): 230/232/234

**5** EXAMPLE 5: synthesis of compounds of formula II.

**5.1** Synthesis of 6-chloro-N,2-dicyclopropyl-5-fluoro-4-pyrimidinamine **31**.

5



10

Cyclopropylamine (11.4 g, 0.200 mol) is added to 4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine **18** (4.80 g, 23 mmol) and the solution is stirred at room temperature for 1 h. The mixture is diluted with diethylether, washed two times with a saturated sodium bicarbonate solution. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford 6-chloro-N,2-dicyclopropyl-5-fluoro-4-pyrimidinamine **31** as a yellow oil (4.99 g, 95 %) which is used in the next step without further purification.

MS ( $M^+$ ): 227/229.

Compounds described in table 3 can be synthesized in an analogous way.

Table 3

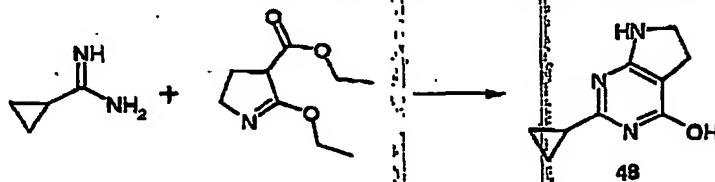
<b>32</b>	6-chloro-N,2-dicyclopropyl-4-pyrimidinamine	MS (MH <sup>+</sup> ): 210/212
<b>33</b>	6-chloro-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine	MS (MH <sup>+</sup> ): 223/225
<b>34</b>	5,6-dichloro-N,2-dicyclopropyl-4-pyrimidinamine	MS (MH <sup>+</sup> ): 244/246/248
<b>35</b>	6-chloro-N,2-dicyclopropyl-5-methoxy-4-pyrimidinamine	MS (MH <sup>+</sup> ): 240/242
<b>36</b>	6-chloro-N,2-dicyclopropyl-5-ethyl-4-pyrimidinamine	MS (MH <sup>+</sup> ): 238/240
<b>37</b>	N-[6-chloro-2-(2-trans-methylcyclopropyl)-4-pyrimidinyl]-N-cyclopropylamine <sup>(i)</sup>	MS (MH <sup>+</sup> ): 224/226
<b>38</b>	N-[6-chloro-2-(2-trans-methylcyclopropyl)-4-pyrimidinyl]-N-cyclopropylamine	MS (MH <sup>+</sup> ): 224/226 [α] <sub>D</sub> <sup>25</sup> = +87.28 (c=1, CH <sub>2</sub> Cl <sub>2</sub> )
<b>39</b>	N-[6-chloro-2-(2-trans-methylcyclopropyl)-4-pyrimidinyl]-N-cyclopropylamine	MS (MH <sup>+</sup> ): 224/226 [α] <sub>D</sub> <sup>25</sup> = -83.80 (c=1, CH <sub>2</sub> Cl <sub>2</sub> )
<b>40</b>	6-chloro-N-cyclopropyl-5-methyl-2-(2-trans-methylcyclopropyl)-4-pyrimidinamine	MS (MH <sup>+</sup> ): 238/240
<b>41</b>	6-chloro-N-cyclopropyl-5-methyl-2-(2-cis-methylcyclopropyl)-4-pyrimidinamine	MS (MH <sup>+</sup> ): 238/240
<b>42</b>	N-[6-chloro-2-(cyclopropylmethyl)-5-methyl-4-pyrimidinyl]-N-cyclopropylamine	MS (MH <sup>+</sup> ): 238/240
<b>43</b>	6-chloro-2-cyclobutyl-N-cyclopropyl-5-methyl-4-pyrimidinamine	MS (MH <sup>+</sup> ): 237/239
<b>44</b>	6-chloro-N,2-dicyclopropyl-5-nitro-4-pyrimidinamine	MS (MH <sup>+</sup> ): 255/257
<b>45</b>	6-chloro-N-cyclobutyl-2-cyclopropyl-5-methyl-4-pyrimidinamine	MS (MH <sup>+</sup> ): 238/240
<b>46</b>	6-chloro-N-cyclopropyl-2-isopropyl-5-methyl-4-pyrimidinamine	MS (MH <sup>+</sup> ): 226/228
<b>47</b>	6-chloro-2-cyclopentyl-N-cyclopropyl-5-methyl-4-pyrimidinamine	MS (MH <sup>+</sup> ): 252/254

(i) compound **37** was resolved into its enantiomers **38** (first eluted) and **39**

- 5 (second eluted) by chromatography on a chiral support (Daicel Chiraldak AD, isopropanol/n-hexane 1/99, 20 °C).

## 6 EXAMPLE 6: synthesis of 4-hydroxypyrimidines of formula XII

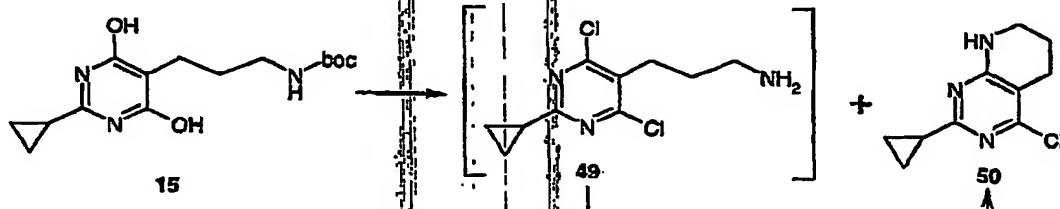
## 6.1 Synthesis of 2-cyclopropyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-ol 48.



5 Sodium (0.417 g, 18.1 mmol) is dissolved in methanol (65 ml) under a nitrogen atmosphere. Cyclopropanecarboximidamide hydrochloride (2.19 g, 18.1 mmol) is added in one portion. The mixture is stirred at room temperature for 0.25 h, then filtered upon hyflocel. The filtrate is concentrated in vacuo to 30 ml. This free base is added to a solution of sodium (0.884 g, 36.2 mmol) in methanol (130 ml) under a nitrogen atmosphere, at room temperature. 2-ethoxy-4,5-dihydro-3H-pyrrrole-3-carboxylic acid ethyl ester (3.4 g, 18.1 mmol) in methanol is added and the mixture is stirred at 60 °C overnight. After cooling, the solvent is evaporated and the solid obtained is dissolved in water. The pH is adjusted at 5 with a 5 N HCl solution and the white precipitate formed is filtered and dried. 2-cyclopropyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-ol 48 (1.88 g, 59 %) is obtained as a white powder and used in the next step without further purification.

MS ( $MH^+$ ): 178.

7 EXAMPLE 7: synthesis of 4-chloropyrimidines of formula X.  
20 7.1 Synthesis of 4-chloro-2-cyclopropyl-5,6,7,8-tetrahydro-5H-pyrido[2,3-d]pyrimidine 50.



25 [3-(2-cyclopropyl-4,6-dihydroxy-pyrimidin-5-yl)-propyl]-carbamic acid tert-butyl ester 15 (1.4 g, 4.5 mmol) is suspended in phosphorus oxychloride (10 ml). A mixture of N,N-diethylaniline (0.744 g, 5 mmol) and phosphorus oxychloride (10 ml) is added dropwise to the suspension at room temperature. The resulting mixture is stirred at 100 °C overnight. The solution is poured onto crushed ice and extracted two times with dichloromethane. The aqueous layer is alkalized using a saturated sodium hydrogenocarbonate solution (pH 8), extracted two times with dichloromethane, reacidified using HCl 5N (pH 3) and extracted again with

dichloromethane. The combined aqueous layers are alkalized (pH 10) and the white precipitate formed is filtered and dried. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford a mixture of 4-chloro-2-cyclopropyl-5,6,7,8-tetrahydro-5*H*-pyrido[2,3-*d*]pyrimidine **50** and non-cyclized 3-(4,6-dichloro-2-cyclopropyl-pyrimidin-5-yl)propylamine **49**. This mixture is dissolved in 1-methoxy-2-propanol and heated at 140 °C for 5 h. After cooling, the solution is diluted with dichloromethane and washed with water (2x) and with an hydrochloric acid solution (1 N). The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. The resulting crude mixture is purified by chromatography on silica gel preparative plates (dichloromethane/ethanol/ammonia 97/3/0.3) to afford a solid, which is combined with the first-formed precipitate. Pure 4-chloro-2-cyclopropyl-5,6,7,8-tetrahydro-5*H*-pyrido[2,3-*d*]pyrimidine **50** is obtained as an orange solid (209 mg, 20%).

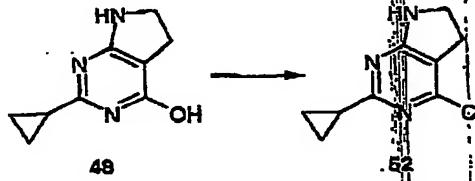
MS (M $H^+$ ): 210/212.

15

4-chloro-2-cyclopropyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]azepine **51** can be synthesized in an analogous way.

MS (M $H^+$ ): 224/226

20 7.2 Synthesis of 4-chloro-2-cyclopropyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine **52**.



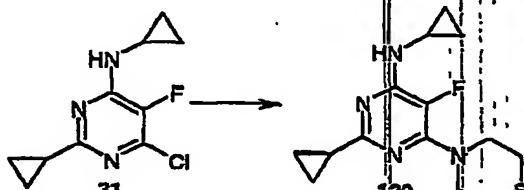
25 **2-cyclopropyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol** **49** (0.5 g, 2.8 mmol) is suspended in phosphorus oxychloride (0.7 ml). A mixture of N,N-diethylaniline (0.46 g, 3.1 mmol) and phosphorus oxychloride (0.7 ml) is added dropwise to the suspension at room temperature. The resulting mixture is stirred at 120 °C for 3 h. The solution is poured onto crushed ice and extracted two times with dichloromethane. The aqueous layer is alkalized (pH 10) and extracted four times with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. The crude mixture (370 mg, 68 %, 91 % purity) is used in the next step without further purification due to the instability of the compound.

30 MS (M $H^+$ ): 196/198

8 EXAMPLE 8: synthesis of compounds of formula I.

8.1 Synthesis of N<sub>2</sub>-dicyclopropyl-5-fluoro-6-(4-thiomorpholiny)-4-pyrimidinamine 120.

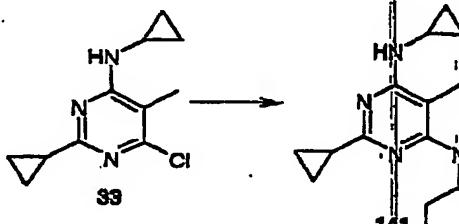
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A mixture of thiomorpholine (2.27 g, 22 mmol) and 6-chloro-N<sub>2</sub>-dicyclopropyl-5-fluoro-4-pyrimidinamine 31 (1 g, 4.4 mmol) is stirred at 110 °C for 18 hours. After cooling, the brown solution is diluted with dichloromethane, washed two times with a saturated sodium bicarbonate solution. The combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to afford a brown oil. The crude oil is purified by column chromatography (hexane/ethyl acetate: 80/20) to give N<sub>2</sub>-dicyclopropyl-5-fluoro-6-(4-thiomorpholiny)-4-pyrimidinamine 120 (915 mg, 71 %) as a yellowish solid.

15

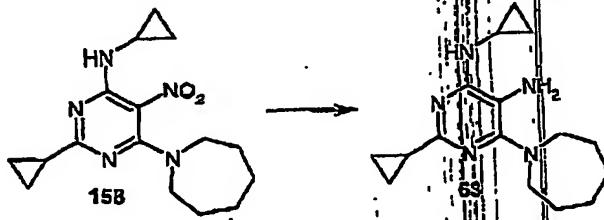
8.2 Synthesis of N<sup>4</sup>-cyclohexyl-N<sup>6</sup>,2-dicyclopropyl-5-methyl-4,6-pyrimidinediamine 141.



20

A mixture of cyclohexylamine (1.78 g, 18 mmol) and 6-chloro-N<sub>2</sub>-dicyclopropyl-5-methyl-4-pyrimidinamine 33 (0.70 g, 3 mmol) in 1-methoxy-2-propanol (2 ml) is stirred at 125 °C for 120 hours. After cooling, the brown solution is diluted with dichloromethane, washed two times with a saturated sodium bicarbonate solution. The combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to afford a brown oil. The crude oil is purified by column chromatography (dichloromethane/methanol: 97.3/2.7) to give pure N<sup>4</sup>-cyclohexyl-N<sup>6</sup>,2-dicyclopropyl-5-methyl-4,6-pyrimidinediamine 141 (0.150 g, 17 %).

8.3      Synthesis of 6-(1-azepanyl)-N<sup>4</sup>,2-dicyclopropyl-4,5-pyrimidinediamine 63.

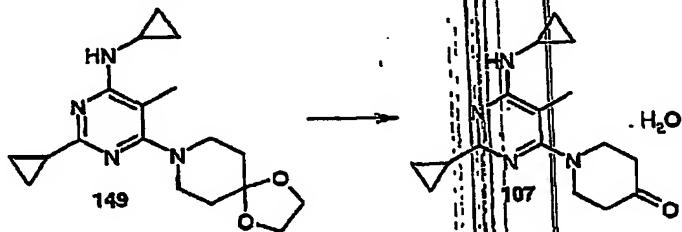


6-(1-azepanyl)-N,2-dicyclopropyl-5-nitro-4-pyrimidinamine 158 was synthesized as described in 6.1. using 6-chloro-N,2-dicyclopropyl-5-nitro-4-pyridinamine 44 and azepane as starting material.

MS (M<sup>+</sup>): 318.

To a suspension of 6-(1-azepanyl)-N,2-dicyclopropyl-5-nitro-4-pyrimidinamine 158 (0.5 g, 1.6 mmol) in 1,4-dioxane (35 ml) and water (35 ml) is added sodium hydrosulfite (2.19 g, 1.8 mmol) and ammonia (25% solution, 1.2 ml). The mixture is stirred at room temperature for 10 h then diluted with ethyl acetate and washed three times with water. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford a yellow oil. The crude oil is purified by column chromatography (dichloromethane/ethanol/ammonia: 95/5/0.5) to give pure 6-(1-azepanyl)-N<sup>4</sup>,2-dicyclopropyl-4,5-pyrimidinediamine 63 (137 mg, 30 %) as a reddish solid.

8.4      Synthesis of 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-piperidinone hydrate 107.

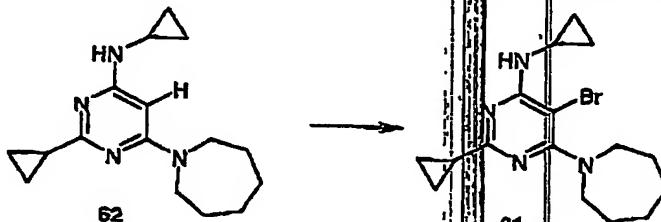


A solution of 1 N HCl (15 ml) is added to a solution of N,2-dicyclopropyl-6-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-methyl-4-pyrimidinamine 149 (285 mg, 0.86 mmol) in tetrahydrofuran (15 ml). The mixture is stirred at room temperature for 18 h, then diluted with dichloromethane and washed three times with sodium bicarbonate. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford a white paste. The compound is dried under vacuum to give pure 1-[2-

cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl-4-piperidinone hydrate **107** (160 mg, 61 %) as a white paste.

8.5 Synthesis of 6-azepan-1-yl-5-bromo-N,2-dicyclopropylpyrimidin-4-amine **61**.

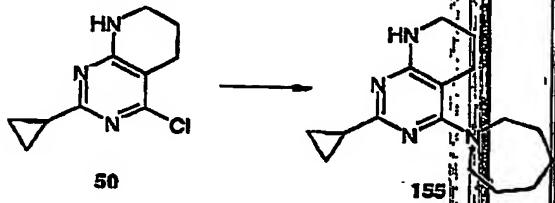
5



N-Bromosuccinimide (0.39 g, 2.2 mmol) is added to a solution of 6-(1-azepanyl)-N,2-dicyclopropyl-4-pyrimidinamine **62** (0.5 g, 1.84 mmol) in chloroform (2 ml). The mixture is stirred at 60 °C overnight then cooled, diluted with dichloromethane and washed two times with water. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. The crude mixture is purified by column chromatography (dichloromethane/ethanol: 97/3) to give pure 6-azepan-1-yl-5-bromo-N,2-dicyclopropylpyrimidin-4-amine **61** (134 mg, 21 %) as a brownish paste.

15

8.6 Synthesis of 4-azepan-1-yl-2-cyclopropyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine **155**.



20

A mixture of azepane (18.2 ml, 142 mmol) and 4-chloro-2-cyclopropyl-5,6,7,8-tetrahydro-5H-pyrido[2,3-d]pyrimidine **50** (0.851 g, 4.06 mmol) is stirred four days at 110 °C. After cooling, the brown solution is diluted with dichloromethane and washed two times with water. The combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to afford a brown oil. The crude oil is purified by column chromatography (dichloromethane/ethanol/ammonia: 90/10/1) to give pure 4-azepan-1-yl-2-cyclopropyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine **155** as a brown solid.

25

Compounds described in table 4 can be synthesized according to one of these methods.

Table 4

Salt and/or solvate	Configuration data	Free base IUPAC NAME	MH <sup>+</sup> (M <sup>+</sup> )	DSC °C (mp)	alpha <sub>d</sub>
53 1 HCl	Achiral	N,2-dicyclopropyl-6-(1,3-thiazolidin-3-yl)-4-pyrimidinamine	(262)	181.3	
54 1 HCl	achiral	N-cyclopropyl-2-isopropyl-6-(1,3-thiazolidin-3-yl)-4-pyrimidinamine	(264)	204.4	
55 1 maleate	achiral	6-(1-azepanyl)-2-cyclobutyl-N-cyclopropyl-5-methyl-4-pyrimidinamine	301		
56 1 maleate	achiral	6-(1-azepanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine	287		
57 9/2	achiral	6-(1-azepanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine	287	149.9	
·maleate	...	6-(1-azepanyl)-N-cyclobutyl-2-cyclopropyl-5-methyl-4-pyrimidinamine	301		
58 1 maleate	achiral	6-(1-azepanyl)-N-cyclobutyl-2-cyclopropyl-5-methyl-4-pyrimidinamine	307	85.2	
59 1 maleate	achiral	6-(1-azepanyl)-5-chloro-2-cyclopropyl-4-pyrimidinyl-1-N-cyclopropylamine			
60 1 maleate	achiral	6-(1-azepanyl)-N,2-dicyclopropyl-5-fluoro-4-pyrimidinamine	291	111.2	
61	achiral	6-azepan-1-yl-5-bromo-N,2-dicyclopropylpyrimidin-4-amine	351/353		
62	achiral	6-(1-azepanyl)-N,2-dicyclopropyl-4-pyrimidinamine	273	124.6	
63	achiral	6-(1-azepanyl)-N <sup>4</sup> ,2-dicyclopropyl-4,5-pyrimidinediamine	288	(76.9)	
64 1 maleate	achiral	6-azepan-1-yl-N-cyclopropyl-2-isopropyl-5-methylpyrimidin-4-amine	289		
65 1 maleate	A-1,2	trans 6-(1-azepanyl)-N-cyclopropyl-5-methyl-2-(2-methylecyclopropyl)-4-pyrimidinamine	301		
66 1 maleate	B-1,2	rac	6-(1-azepanyl)-N-cyclopropyl-5-methyl-2-(2-methylecyclopropyl)-4-pyrimidinamine	301	

67		B-18,28	pure	<i>trans</i>	6-[1-azepanyl]-N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-4-pyrimidinamine	301	-58.79
68	A-18,28	Pure	<i>trans</i>	6-[1-azepanyl]-N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-4-pyrimidinamine	301	+57.65	
69	1 maleate	achiral		6-[1-azepanyl]-N-cyclopropyl-2-(cyclopropylmethyl)-5-methyl-4-pyrimidinamine	301		
70	A-1,2	rac	<i>trans</i>	N-[6-(1-azepanyl)-5-chloro-2-(2-methylcyclopropyl)-4-pyrimidinyl]-N-cyclopropylamine	321		
71	A-1,2	rac	<i>trans</i>	6-[1-azepanyl]-N-cyclopropyl-2-(2-methylcyclopropyl)-4-pyrimidinamine	287		
72	0.2 iPrOH, 1 maleate	achiral		6-[1-azocanyl]-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine	301		
73	A-1,2	rac	<i>trans</i>	6-[1-azocanyl]-N-cyclopropyl-2-(2-methylcyclopropyl)-4-pyrimidinamine	301	-108.5	
74	...	3,5-mkt		N,2-dicyclopropyl-6-(3,5-dimethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine	301	91.2	
75	1 maleate	achiral		N,2-dicyclopropyl-6-[4-(2-methoxyphenyl)-1-piperidinyl]-5-methyl-4-pyrimidinamine	379	123.6	
76	1 iPrOH, 1 maleate	achiral		[1-[2-cyclopropyl-5-methyl-6-[4-(trifluoromethyl)piperidinyl]-5-methyl-4-piperidinyl](diphenyl)methanol	455	86.1	
77		achiral		N,2-dicyclopropyl-5-methyl-6-[4-(trifluoromethyl)piperidinyl]-5-methyl-4-pyrimidin-4-amine	341	(86.4)	
78	1 maleate	achiral		N,2-dicyclopropyl-6-[4-(4-difluoro-1-piperidinyl)-5-methyl-4-pyrimidinamine	309	121.9	

79		achiral	N-[2-dicyclopropyl-6-(4,4-dimethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine	301	
80	1 HCl	achiral	N-[2-dicyclopropyl-6-(4,4-dimethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine	301	
81		achiral	1-[2-dicyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-piperidinecarboxamide	316	230.6
82	1 maleate	achiral	6-(4-benzyl-1-piperidinyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine	363	132.1
83		achiral	1-[2-dicyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-piperidinecarboxylic acid	317	219.6
84		achiral	1-[2-dicyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-phenyl-4-piperidinecarbonitrile	374	145.3
85	1 maleate	achiral	ethyl 1-[2-dicyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-piperidinecarboxylate	345	118.9
86		achiral	N-[2-dicyclopropyl-6-(4-ethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine	301	
87	1 HCl	achiral	N-[2-dicyclopropyl-6-(4-ethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine	301	
88		achiral	N-[2-dicyclopropyl-6-(4-ethyl-4-methyl-1-piperidinyl)-5-methyl-4-pyrimidinamine	315	
89	1 HCl	achiral	N-[2-dicyclopropyl-6-(4-ethyl-4-methyl-1-piperidinyl)-5-methyl-4-pyrimidinamine	289	150.0
90		achiral	1-[2-dicyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-piperidinol	365	
91		achiral	1-[2-dicyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-phenyl-4-piperidinol		

92		achiral	1-[2-cyclopropyl-6-(cyclopropylamino)-5-fluoro-4-pyrimidinyl]-4-phenyl-4-piperidinol	369		
93		achiral	(1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-piperidinyl)methanol	303	113.9	
94	1 maleate	achiral	N,2-dicyclopropyl-5-ethyl-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	301		
95	1 maleate	achiral	N,2-dicyclopropyl-5-methyl-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	287	97.9	
96		achiral	N,2-dicyclopropyl-5-fluoro-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	291		
97	A-1,2	rac	trans N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	301	91.3	
98	1 maleate	B-1,2	rac cis N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	301		
99	A-	pure	trans N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	301	61.65	
100	-B-	pure	trans N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	301	63.51	
101		A-1,2	trans N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	287	120.3	
102	1 HCl	A-1,2	trans N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	287	148.1	
103	1 maleate	A-1,2	trans N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	287	132.1	
104	A-	pure	trans N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine	287	65.61	
		18.2g				

105	B- 1S,2S	pure	trans	N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-	287		-70.6
106	1 HCl	achiral		pyrimidinamine N,2-dicyclopropyl-5-methyl-6-(4-methylene-1-piperidinyl)-4-	285		
107	1 H <sub>2</sub> O	achiral		pyrimidinamine 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-piperidinyl]-4-	305		
108		achiral		piperidinone 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-piperidinyl]-4-	329		
109	1 maleate	achiral		N <sup>4</sup> ,2-dicyclopropyl-N <sup>6</sup> ,5-dimethyl-N <sup>6</sup> -(2-(2-thienyl)ethyl)-4,6-	315	129.1	
110	1 maleate	achiral		pyrimidinediamine N <sup>4</sup> ,2-dicyclopropyl-5-methyl-N <sup>6</sup> -(2-(2-thienyl)ethyl)-4,6-	299		
111	1 maleate	achiral		pyrimidinediamine N <sup>4</sup> ,2-dicyclopropyl-5-methyl-N <sup>6</sup> -(2-furylmethyl)-N <sup>6</sup> ,5-dimethyl-4,6-	301	151.9	
112	1 maleate	achiral		pyrimidinediamine N <sup>4</sup> ,2-dicyclopropyl-6-(3,6-dihydro-1(2H)-pyridinyl)-5-methyl-4-	271	118.9	
113	A-1,2	rac	trans	N-cyclopropyl-6-(3,6-dihydro-1(2H)-pyridinyl)-2-(2-methylcyclopropyl)-4-	271	107.4	
114	1 HCl	A-1,2	rac	pyrimidinamine N-cyclopropyl-6-(3,6-dihydro-1(2H)-pyridinyl)-2-(2-methylcyclopropyl)-4-	271		
115	1 maleate	achiral		6-(3-azabicyclo[3.2.1]oct-3-yl)-N,2-dicyclopropyl-5-methyl-4-	299		
				pyrimidinamine			

116	1 maleate	achiral		N <sup>4</sup> ,2-dicyclopropyl-5-methyl-N <sup>6</sup> -(4-pyridinylmethyl)-4,6-pyrimidinediamine	296	165.3
117	2 maleate	A-1,2	rac	trans N <sup>4</sup> -cyclopropyl-2-(2-methylcyclopropyl)-N <sup>6</sup> -(4-pyridinylmethyl)-4,6-pyrimidinediamine	296	
118	1 maleate			achiral N,2-dicyclopropyl-5-ethyl-6-(4-thiomorpholiny)-4-pyrimidinediamine (1:1)	305	99.5
119	1 HCl			achiral N,2-dicyclopropyl-5-methyl-6-(4-thiomorpholiny)-4-pyrimidinediamine	(290)	224.4
120				achiral N,2-dicyclopropyl-5-fluoro-6-(4-thiomorpholiny)-4-pyrimidinediamine	295	(87)
121				achiral N,2-dicyclopropyl-6-(4-thiomorpholiny)-4-pyrimidinediamine	(276)	
122				achiral N,2-dicyclopropyl-5-methoxy-6-(4-thiomorpholiny)-4-pyrimidinediamine	307	
123	1 maleate			achiral N-cyclopropyl-2-isopropyl-5-pentyl-6-(4-thiomorpholiny)-4-pyrimidinediamine	293	89.64
124	1 HCl	A-	pure	trans N-cyclopropyl-5-methyl-2-(2-methylcyclononyl)-6-(4-thiomorpholiny)-4-pyrimidinediamine	(304)	+48.7
125	1 HCl	B-	16.28	trans N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-thiomorpholiny)-4-pyrimidinediamine	(304)	-52.0
126	1 HCl	A-	16.28	pure trans N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-thiomorpholiny)-4-pyrimidinediamine	(290)	+66.9
127	1 HCl	B-	16.28	pure trans N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-thiomorpholiny)-4-pyrimidinediamine	(290)	-68.6
128	1 maleate	achiral		N <sup>4</sup> -benzyl-N <sup>6</sup> ,2-dicyclopropyl-5-methyl-4,6-pyrimidinediamine	295	
129	1 maleate	achiral		N <sup>4</sup> -benzyl-N <sup>6</sup> ,2-dicyclopropyl-N <sup>4</sup> ,5-dimethyl-4,6-pyrimidinediamine	309	74.5

					(294)	
130	1 HBr	A-1,2	rac	trans N <sup>4</sup> -benzyl-N <sup>6</sup> -cyclopropyl-2-(2-methylcyclopropyl)-4,6-pyrimidinediamine	341	132.7
131	1 maleate		achiral	N <sup>4</sup> ,2-dicyclopropyl-5-methyl-N <sup>6</sup> -[2-(methylsulfanyl)benzyl]-4,6-pyrimidinediamine	391	162.7
132	1 maleate		achiral	N <sup>4</sup> ,2-dicyclopropyl-N <sup>6</sup> -(2,6-difluorobenzyl)-5-methyl-4,6-pyrimidinediamine	313	141.9
133	1 maleate		achiral	N <sup>4</sup> ,2-dicyclopropyl-N <sup>6</sup> -(2-fluorobenzyl)-5-methyl-4,6-pyrimidinediamine	354	
134	1 HCl	A-1,2	rac	trans N <sup>4</sup> -cyclopropyl-N <sup>6</sup> -methyl-2-(2-methylcyclopropyl)-N <sup>6</sup> -(2-nitrobenzyl)-4,6-pyrimidinediamine	431	170.8
135	1 maleate		achiral	N <sup>4</sup> -(3,5-bis(trifluoromethyl)benzyl)-N <sup>6</sup> -2-dicyclopropyl-5-methyl-4,6-pyrimidinediamine	331	184.9
136	1 maleate		achiral	N <sup>4</sup> ,2-dicyclopropyl-N <sup>6</sup> -(3,5-difluorobenzyl)-5-methyl-4,6-pyrimidinediamine	301	136.1
137	1 maleate		achiral	N <sup>4</sup> -cycloheptyl-N <sup>6</sup> ,2-dicyclopropyl-5-methyl-4,6-pyrimidinediamine	301	
138	1 maleate	A-1,2	rac	trans N <sup>4</sup> -cycloheptyl-N <sup>6</sup> -cyclopropyl-2-(2-methylcyclopropyl)-4,6-pyrimidinediamine	301	
139	1 maleate		achiral	N <sup>4</sup> -cyclohexyl-N <sup>6</sup> ,2-dicyclopropyl-N <sup>4</sup> ,5-dimethyl-4,6-pyrimidinediamine	307/309	62.9
140	1 maleate		achiral	5-chloro-N <sup>4</sup> -cyclohexyl-N <sup>6</sup> ,2-dicyclopropyl-4,6-pyrimidinediamine	287	159.7
141	1 maleate		achiral	N <sup>4</sup> -cyclohexyl-N <sup>6</sup> ,2-dicyclopropyl-5-methyl-4,6-pyrimidinediamine		

142	1 maleate	A-1,2	rac	trans	$N^4$ -cyclohexyl- $N^6$ -cyclopropyl-2-(2-methylcyclopropyl)-4,6-pyrimidinediamine	287	174.3
143	A-	pure	trans	$N^4$ -cyclohexyl- $N^6$ -cyclopropyl-2-(2-methylcyclopropyl)pyrimidine-4,6-diamine	287	65.25	
144	B-	pure	trans	$N^4$ -cyclohexyl- $N^6$ -cyclopropyl-2-(2-methylcyclopropyl)pyrimidine-4,6-diamine	287	-54.4	
145	1 maleate	mixt	cis & trans	$N^4$ ,2-dicyclopropyl-5-methyl- $N^6$ -(4-methylcyclohexyl)-4,6-pyrimidinediamine	301	166.0	
146	A	pure	cis or trans	$N^4$ ,2-dicyclopropyl-5-methyl- $N^6$ -(4-methylcyclohexyl)-4,6-pyrimidinediamine	301		
147			achiral	1-[2-cyclopropyl-6-(cyclopropylamino)-5-methylpyrimidin-4-yl]azepan-2-one	301		
148	1 maleate		achiral	$N^4$ -2-dicyclopropyl-6-(3,4-dihydro-2(H)-isquinolonyl)-5-methyl-4-pyrimidinamine	321	196.0	
149			achiral	$N^4$ ,2-dicyclopropyl-6-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-methyl-4-pyrimidinamine	331	111.0	
150	1 maleate		achiral	$N^4$ ,2-dicyclopropyl-5-methyl-2-(2-diphenylethyl)-5-methyl-4,6-pyrimidinediamine	385	157.4	
151	1 maleate	1,5	mixt	$N^4$ ,2-dicyclopropyl-5-methyl-6-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)-4-pyrimidinamine	341		
152	1 maleate	A-4a,8a	rac	$N^4$ ,2-dicyclopropyl-5-methyl-6-octahydro-2(1H)-isoquinolonyl-4-pyrimidinamine	327		

<b>153</b>	1 HCl	achiral	N-[6-(8-azaspiro[4.5]dec-8-yl]-2-cyclopropyl-5-methyl-4-pyrimidinyl]-N-cyclopropylamine	327	
<b>154</b>	1 maleate	achiral	6-(1-azepanyl)-2-cyclopentyl-N-cyclopropyl-5-methyl-4-pyrimidinamine	315	
<b>155</b>		achiral	4-azepan-1-yl-2-cyclopropyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine	273	
<b>156</b>		achiral	4-azepan-1-yl-2-cyclopropyl-6,7,8,9-tetrahydro-pyrido[4,5-h]azepine	287	
<b>157</b>		achiral	4-azepan-1-yl-2-cyclopropyl-6,7-dihydro-pyrido[2,3-d]pyrimidine		

Compound **97** was resolved into its enantiomers by chromatography on a chiral support (Chiralpak AD Daicel, isopropanol/isohexane/diethylamine 5/95/0.1 (v/v), 30 °C) to give compound **99** (first eluted) and compound **100** (second eluted). Compound **65** was resolved into its enantiomers by chromatography on a chiral support (Chiralpak AD Daicel, isopropanol/isohexane/diethylamine 5/95/0.1, 30 °C) to give compound **67** (second eluted) and compound **68** (first eluted).

Compound **142** was resolved into its enantiomers by chromatography on a chiral support (Chiralpak AD Daicel, isopropanol/isohexane/diethylamine 3/97/0.1, 30 °C) to give compound **143** (first eluted) and compound **144** (second eluted). Compound **101** was resolved into its enantiomers by chromatography on a chiral support (Chiralpak AD Daicel, isopropanol/methane mixture 4/96/30 °C) to give compound **104** (first eluted) and compound **105** (second eluted).

9        EXAMPLE 9: affinity for human muscarinic receptors.

Chinese Hamster Ovarian cells (CHO) expressing the human recombinant m1, m2, m3, m4 and m5 receptors were cultured in Ham's F12 media supplemented with 100 IU/ml of penicillin, 100 µg/ml of streptomycin, 400 µg /ml of geneticin and 5 % of fetal bovine serum. Cell cultures were maintained in a humidified incubator at 37 °C and 5 % CO<sub>2</sub>.

Confluent CHO cells expressing human m1, m2, m3, m4 and m5 muscarinic receptors were harvested and resuspended in phosphate buffered saline without calcium and magnesium. The cell suspension was centrifuged at 1500 x g for 3 min (4 °C). The cell pellet was homogenized in a 15 mM Tris-HCl (pH 7.5) buffer containing 2 mM MgCl<sub>2</sub>, 0.3 mM EDTA and 1 mM EGTA. The crude membrane fraction was collected by two consecutive centrifugation steps at 40.000 x g for 25 min (4 °C). The final pellet was resuspended, at a protein concentration ranging from 2 to 6 mg/ml, in a 7.5 mM Tris-HCl (pH 7.5) buffer containing 12.5 mM MgCl<sub>2</sub>, 0.3 mM EDTA, 1 mM EGTA and 250 mM sucrose and stored in liquid nitrogen.

Binding assays were performed according to procedure described in: Buckley N.J., Bonner T.I., Buckley C.M., Brann M.R., Mol. Pharmacol. (1989), 35, 469-476, but with slight modifications.

Briefly, 25 to 50 µg of membrane proteins were incubated at room temperature in 1 ml of a 50 mM Tris-HCl (pH 7.4) buffer containing 2 mM of MgCl<sub>2</sub>, 0.1 nM of [<sup>3</sup>H]-NMS (N-methylscopolamine, 85 Ci/mmol, from Apbotech, UK) and increasing concentrations of test compound dissolved in DMSO (1 % final concentration). Non specific binding was measured in the presence of 1 µM atropine. After 60 (m2) or 120 (m3) min. incubation, assays were stopped by rapid vacuum filtration of the samples through glass fiber filters (Filtermat A, Wallac, Belgium) presoaked in 0.3 % polyethyleneimine for at least 2 h. Samples were further rinsed with 8 ml of ice-cold 50 mM Tris-HCl (pH 7.4) buffer. Radioactivity trapped onto the filter was counted in a Betaplate counter (Wallac). Competition binding curves were analyzed by non-linear regression with XLfit software (JDBS, UK).

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10        EXAMPLE 10: PDE IV enzymatic activity.

*Enzyme source:*

Cytosolic fraction from U937 cells pre-stimulated for 4 h at 37 °C with a mixture of rolipram 30 µM and salbutamol 1 µM (Torphy T.J., Zhou H.L., Cieslinski L.B., J. Pharmacol. Exp. Ther. (1992), 263(3), 195-1205).

*SPA Phosphodiesterase assay (Amersham Pharmacia Biotech; Belgium):*

Assays were performed in 100  $\mu$ L of 50 mM Tris HCl buffer (pH 7.4) containing 5 mM MgCl<sub>2</sub>, 2 mM EGTA, 20 nM of [<sup>3</sup>H]-cAMP (40-60 Ci/mmol), the cytosolic fraction of 50,000 U937 cells and the appropriate concentration of test compound (usually 10  $\mu$ M) dissolved in DMSO (final assay concentration not exceeding 1 %). After 5 30 min incubation at room temperature, 0.5  $\mu$ g of SPA yttrium silicate beads are added to each sample. Radioactivity bound to the beads (5'-AMP) is determined by liquid scintillation. Non PDE IV activity and/or non specific binding of the labeled substrate to the SPA beads is defined as the residual radioactivity remaining in the 10 presence of rolipram 32  $\mu$ M (non PDE IV activity represents about 40 % of total activity). PDE IV activity is determined by subtracting the non PDE IV activity from the total activity.

Compounds according to the invention showed pIC<sub>50</sub> values ranging from 6.5 15 to 10 for the m<sub>3</sub> receptor, and showed pIC<sub>50</sub> values ranging from 5.7 to 8 for PDE IV. Dual high affinities were especially shown by compounds 56, 57, 59, 61, 62, 63, 64, 65, 66, 67, 72, 77, 78, 79, 80, 86, 87, 94, 95, 98, 106, 112, 115, 118, 119, 132, 144, 145, 154, 155 and 156.

20 11 EXAMPLE 11: *in vitro* inhibition of carbachol-induced contraction of guinea-pig trachea.

The method was developed according to the procedure described in Leff P., Dougall I.G., Harper D., Br. J. Pharmacol. (1993), 110, 239-244. Tracheal rings were prepared from male Dunkin-Hartley guinea pig. Tissues were mounted in 20 ml organ 25 baths containing modified Krebs' solution in the presence of 3.10<sup>-6</sup> M indomethacin, 3.10<sup>-4</sup> M hexamethonium and 10<sup>-6</sup> M propranolol. The bathing solution was maintained at 37 °C and gassed with 95 % O<sub>2</sub>-5 % CO<sub>2</sub>. Tissues were allowed to equilibrate for a period of 60 min under a resting tension of 1 g. Isometric contractions were measured by force-displacement transducers coupled to an IOX computer system capable of controlling automatic data acquisition and bath washout by automatic fluid circulation through electrovalves at defined times. Drugs were manually or robotically 30 injected into the bath according to the stability of the measured signal.

At the end of the 60 min period of stabilisation, the tracheas were contracted twice with 10<sup>-6</sup> M carbachol at 30 min intervals. Two cumulative concentration-response curves were successively constructed in the absence or presence of the test compound (incubation time: 1 hour). Results were obtained from at least 3 or 4 individual experiments. Control tissues were treated with the solvent.

Antagonistic potency of the test compound was estimated by the calculation of pD<sub>2</sub>'s and /or pA<sub>2</sub> values according to the methods described by Van Rossum (Van Rossum J.M., Hurkmans J.A.T.M., Wolters C.J.J., Arch. Int. Pharmacodyn. Ther. (1963), 143, 299-330) or Arunlakshana & Schild (Arunlakshana O., Schild H.O., Br. J. Pharmacol. (1959), 14, 48-58).

Preferred compounds according to the invention show pA<sub>2</sub> values typically ranging from 5.5 to 8.

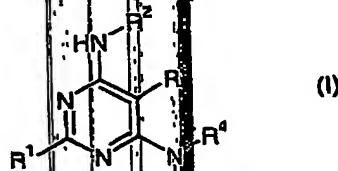
In the tables, the stereochemical information is contained in the three columns headed 'configuration data'. The second column indicates whether a compound has no stereogenic center (ACHIRAL), is a pure configuration isomer or enantiomer (PURE), a racemate (RAC) or is a mixture of two or more stereoisomers, possibly in unequal proportions (MIXT). The first column contains the stereochemical assignment for each recognised center, following the IUPAC numbering used in the preceding column. A number alone indicates the existence of both configurations at that center. A number followed by 'R' or 'S' indicates the known absolute configuration at that center. A number followed by 'S' indicates the existence of only one but unknown absolute configuration at that center. The letter (A, B, C, D) in front is a way of distinguishing the various configuration isomers, enantiomers or racemates of the same structure.

The third column precises the cis or trans isomerism.

In the tables, the melting points are in most cases determined by the onset of the DSC curve. When a visual (fusionometer) melting point is given, the value is between brackets.

## Claims:

1. A compound having the formula I, or a pharmaceutically acceptable salt thereof.



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wherein

 $R^1$  is alkyl or cycloalkyl, $R^2$  is cycloalkyl, $R^3$  is hydrogen, alkyl, halogen, hydroxy, alkoxy or amino,  
or  $R^2R^3$  is an alkylene bridging group,

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 $R^4$  is hydrogen or alkyl, $R^5$  is cycloalkyl, arylalkyl or heterocycle-alkyl,or  $NR^4R^5$  is an heterocycle, which may be substituted, containing only one  
heteroatom which is a nitrogen atom or containing two heteroatoms wherein  
one is a nitrogen atom and the other is a non-oxidized sulfur atom.

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with the proviso that when  $R^2R^3$  is an alkylene bridging group,  $R^1$  is a  
cycloalkyl.

2. A compound according to claim 1, wherein

20  $R^1$  is alkyl or C3-7-cycloalkyl, $R^2$  is C3-7-cycloalkyl, $R^3$  is hydrogen, C1-4-alkyl, halogen, hydroxy, alkoxy or amino,  
or  $R^2R^3$  is a C2-4 alkylene bridging group. $R^4$  is hydrogen or alkyl,25  $R^5$  is C3-7-cycloalkyl, arylalkyl or heterocycle-alkyl,or  $NR^4R^5$  is a heterocycle, which may be substituted, containing only one  
heteroatom which is a nitrogen atom or containing two heteroatoms wherein  
one is a nitrogen atom and the other is a non-oxidized sulfur atom.with the proviso that when  $R^2R^3$  is an alkylene bridging group,  $R^1$  is a  
cycloalkyl.

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3. A compound according to any of the preceding claims wherein R<sup>1</sup> is C3-4 alkyl or C3-4 cycloalkyl.
4. A compound according to claim 3 wherein R<sup>1</sup> is selected from the group of cyclopropyl, isopropyl, cyclobutyl, cyclopentyl, 2-methyl-cyclopropyl and cyclopropylmethyl.
5. A compound according to any of the preceding claims wherein R<sup>2</sup> is C3-4 cycloalkyl.
- 10 6. A compound according to claim 5 wherein R<sup>2</sup> is selected from cyclopropyl or cyclobutyl.
7. A compound according to any of the preceding claims wherein R<sup>3</sup> is hydrogen, methyl, ethyl, a Cl atom, a F atom, a Br atom, amino or methoxy.
- 15 8. A compound according to any of claims 1-4 wherein R<sup>2</sup>R<sup>3</sup> is an alkylene bridging group selected from ethylene, propylene and butylene.
- 20 9. A compound according to any of the preceding claims wherein R<sup>4</sup> is hydrogen or C1-4 alkyl.
10. A compound according to claim 9 wherein R<sup>4</sup> is hydrogen or methyl.
- 25 11. A compound according to any of the preceding claims wherein R<sup>5</sup> is 2-(2-thienyl)ethyl, 2-furylmethyl, 2-thienylmethyl, 4-pyridinylmethyl, benzyl, 2-(methylsulfanyl)benzyl, 2,6-difluorobenzyl, 2-fluorobenzyl, 2-nitrobenzyl, 3,5-bis(trifluoromethyl)benzyl, 3,5-difluorobenzyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, or 2,2-diphenylethyl.
- 30 12. A compound according to any of claims 1-8 wherein NR<sup>4</sup>R<sup>5</sup> is 1,3-thiazolidin-3-yl, 1-azepanyl, 1-azocanyl, 3,5-dimethyl-1-piperidinyl, 4-(2-methoxyphenyl)-1-piperidinyl, 4-(hydroxy(diphenyl)methyl)-1-piperidinyl, 4-(trifluoromethyl)-1-piperidinyl, 4,4-difluoro-1-piperidinyl, 4,4-dimethyl-1-piperidinyl, 4-amido-1-piperidinyl, 4-benzyl-1-piperidinyl, 4-carboxy-1-piperidinyl, 4-cyano-4-phenyl-1-piperidinyl, 4-ethoxycarbonyl-1-piperidinyl, 4-ethyl-1-piperidinyl, 4-ethyl-4-

methyl-1-piperidinyl, 4-hydroxy-1-piperidinyl, 4-hydroxy-4-phenyl-1-piperidinyl, 4-hydroxymethyl-1-piperidinyl, 4-methyl-1-piperidinyl, 4-methylene-1-piperidinyl, 4-one-1-piperidinyl, 3,6-dihydro-1(2H)-pyridinyl, 3-azabicyclo[3.2.1]oct-3-yl, 4-pyridinylmethyl, 4-thiomorpholinyl, 2-one-1-azepanyl, 3,4-dihydro-2(1H)-isoquinolines, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl, 1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl, octahydro-2(1H)-isoquinolinyl or 8-azaspiro[4.5]dec-8-yl.

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13. A compound selected from 6-(1-azepany)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N-[6-(1-azepany)-5-chloro-2-cyclopropyl-4-pyrimidinyl]-N-cyclopropylamine; 6-azepan-1-yl-5-bromo-N,2-dicyclopropylypyrimidin-4-amine; 6-(1-azepanyl)-N,2-dicyclopropyl-4-pyrimidinamine; 6-(1-azepanyl)-N<sup>4</sup>,2-dicyclopropyl-4,5-pyrimidinediamine; 6-azepan-1-yl-N-cyclopropyl-2-isopropyl-5-methylpyrimidin-4-amine; 6-(1-azepanyl)-N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-4-pyrimidinamine; 6-(1-azocanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-[4-(trifluoromethyl)piperidin-1-yl]-pyrimidin-4-amine; N,2-dicyclopropyl-6-(4,4-difluoro-1-piperidiny)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-6-(4,4-dimethyl-1-piperidiny)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-6-(4-ethyl-1-piperidiny)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-ethyl-6-(4-methyl-1-piperidiny)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-methyl-1-piperidiny)-4-pyrimidinamine; N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidiny)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-methylene-1-piperidiny)-4-pyrimidinamine; N,2-dicyclopropyl-6-(3,6-dihydro-1(2H)-pyridinyl)-5-methyl-4-pyrimidinamine; 6-[3-azabicyclo[3.2.1]oct-3-yl]-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-ethyl-6-(4-thiomorpholiny)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-thiomorpholiny)-4-pyrimidinamine; N<sup>4</sup>,2-dicyclopropyl-N<sup>6</sup>-(2,6-difluorobenzyl)-5-methyl-4,6-pyrimidinediamine; N<sup>4</sup>-cyclohexyl-N<sup>6</sup>-cyclopropyl-2-(2-methylcyclopropyl)pyrimidine-4,6-diamine; N<sup>4</sup>,2-dicyclopropyl-5-methyl-6-(4-methylcyclohexyl)-4,6-pyrimidinediamine; 6-(1-azepanyl)-N-cyclopentyl-2-cyclopropyl-5-methyl-4-pyrimidinamine; 4-azepan-1-yl-2-cyclopropyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine and 4-azepan-1-yl-2-cyclopropyl-6,7,8,9-tetrahydro-pyrimido[4,5-b]azepine, or pharmaceutically acceptable salts thereof.

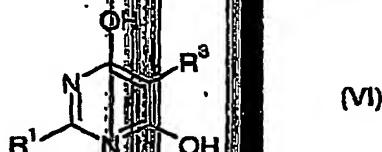
14. A compound selected from 6-(1-azepanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N-[6-(1-azepanyl)-5-chloro-2-cyclopropyl-4-pyrimidinyl]-N-cyclopropylamine; 6-azepan-1-yl-5-bromo-N,2-dicyclopropylpyrimidin-4-amine; 6-(1-azepanyl)-N<sup>4</sup>,2-dicyclopropyl-4,5-pyrimidinediamine; 6-azepan-1-yl-N-cyclopropyl-2-isopropyl-5-methylpyrimidin-4-amine; 6-(1-azepanyl)-N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-4-pyrimidinamine; 6-(1-azocanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-[4-(trifluoromethyl)piperidin-1-yl]pyrimidin-4-amine; N,2-dicyclopropyl-6-(4,4-difluoro-1-piperidinyl)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-6-(4,4-dimethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-6-(4-ethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-ethyl-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine; N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1-piperidinyl)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-methylene-1-piperidinyl)-4-pyrimidinamine; N,2-dicyclopropyl-6-(3,4-dihydro-1(2H)-pyridinyl)-5-methyl-4-pyrimidinamine; 6-(3-azabicyclo[3.2.1]oct-3-yl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine; N,2-dicyclopropyl-5-cyclohexyl-6-(4-thiomorpholiny)-4-pyrimidinamine; N,2-dicyclopropyl-5-methyl-6-(4-thiomorpholiny)-4-pyrimidinamine; N<sup>4</sup>,2-dicyclopropyl-N<sup>6</sup>(2,6-difluorobenzyl)-5-methyl-4,6-pyrimidinediamine; N<sup>4</sup>,2-dicyclopropyl-5-methyl-N<sup>6</sup>-(4-methylcyclohexyl)-4,6-pyrimidinediamine; 6-(1-azepanyl)-N-(C<sub>1</sub>-C<sub>6</sub>-alkenyl)-2-cyclopropyl-5-methyl-4-pyrimidinamine; 4-azepan-1-yl-2-cyclopropyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine and 4-azepan-1-yl-2-cyclopropyl-6,7,8,9-tetrahydro-pyrimido[4,5-b]azepine, or pharmaceutically acceptable salts thereof.
15. A compound according to any preceding claims as a pure enantiomer.
16. A pharmaceutical composition comprising an effective amount of a compound according to any preceding claim in combination with a pharmaceutically acceptable diluent or carrier.
17. A pharmaceutical composition according to claim 16 for administration by inhalation.
18. A compound according to any of claims 1-15 or a pharmaceutically acceptable salt thereof for use as a medicament.

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19. The use of a compound according to any of claims 1-15 for the manufacture of  
a medicament for the treatment of respiratory disorders in connection with  
Chronic Obstructive Pulmonary Disease or for treatment of symptoms related  
to chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis,  
adult respiratory distress syndrome, rhinitis or asthma.
- 10 20. A method for treating respiratory disorders in connection with Chronic  
Obstructive Pulmonary Disease or for treating symptoms related to chronic  
bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult  
respiratory distress syndrome, rhinitis or asthma comprising administering at  
least one compound according to claims 1-15 or a pharmaceutically acceptable  
salt thereof to a patient.
- 15 21. A compound of formula II, or a pharmaceutically acceptable salt thereof,
- (II)
- wherein
- R<sup>1</sup> is alkyl or cycloalkyl;
- R<sup>2</sup> is cycloalkyl; and
- 20 R<sup>3</sup> is hydrogen, alkyl, halogen, alkoxy or hydroxy.
22. A compound of formula II selected from the group consisting of 6-chloro-N,2-dicyclopropyl-5-fluoro-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine, 5,6-dichloro-N,2-dicyclopropyl-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-5-methoxy-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-5-ethyl-4-pyrimidinamine, N-[6-chloro-2-(2-trans-methylcyclopropyl)-4-pyrimidinyl]-N-cyclopropylamine and its enantiomers, 6-chloro-N-cyclopropyl-5-methyl-2-(2-trans-methylcyclopropyl)-4-pyrimidinamine, 6-chloro-N-cyclopropyl-5-methyl-2-(2-cis-methylcyclopropyl)-4-pyrimidinamine, N-[6-chloro-2-(cyclopropylmethyl)-5-methyl-4-pyrimidinyl]-N-cyclopropylamine, 6-chloro-2-cyclobutyl-N-cyclopropyl-5-methyl-4-pyrimidinamine, 6-chloro-N,2-dicyclopropyl-5-nitro-4-pyrimidinamine, 6-chloro-N-cyclobutyl-2-cyclopropyl-5-

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methyl-4-pyrimidinamine, 6-chloro-N-cyclopropyl-2-isopropyl-5-methyl-4-pyrimidinamine and 6-chloro-2-cyclopropyl-N-cyclopropyl-5-methyl-4-pyrimidinamine.

- 5 23. 2-methylcyclopropanecarboxamide  
 24. A compound of formula VI, or a pharmaceutically acceptable salt thereof.



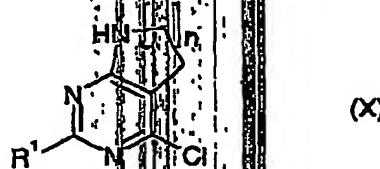
wherein

10 R<sup>1</sup> is alkyl or cycloalkyl, and  
 R<sup>3</sup> is alkoxy.

25. A compound of formula VI selected from the group consisting of 2-cyclopropyl-5-fluoro-4,6-pyrimidinediol, 5-fluoro-2-cyclopropyl-4,6-pyrimidinediol, 2-cyclopropyl-5-methoxy-4,6-pyrimidinediol, 2-cyclopropyl-5-ethyl-4,6-pyrimidinediol, 2-(2-methylcyclopropyl)-4,6-pyrimidinediol, 5-methyl-2-(2-methylcyclopropyl)-4,6-pyrimidinediol, 2-(cyclopropylmethyl)-5-methyl-4,6-pyrimidinediol, 2-cyclobutyl-5-methyl-4,6-pyrimidinediol, 2-cyclopentyl-5-methyl-4,6-pyrimidinediol, [3-(2-cyclopropyl-4,6-dihydroxy-pyrimidin-5-yl)-propyl]-carbamic acid tert-butyl ester, [2-(2-cyclopropyl-4,6-dihydroxy-pyrimidin-5-yl)-butyl]-carbamic acid tert-butyl ester.
- 20 26. A compound selected from the group consisting of 4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine, 4,5,6-trichloro-2-(cyclopropyl)pyrimidine, 4,6-dichloro-2-cyclopropyl-5-pyrimidinyl methyl ether, 4,6-dichloro-2-cyclopropyl-5-ethylpyrimidine, 4,6-dichloro-2-(2-methylcyclopropyl)pyrimidine, 4,6-dichloro-2-methyl-2-(2-methylcyclopropyl)pyrimidine, 4,6-dichloro-2-(cyclopropylmethyl)-5-methylpyrimidine, 4,6-dichloro-2-cyclobutyl-5-methylpyrimidine, 4,6-dichloro-2-isopropyl-5-methylpyrimidine and 4,6-dichloro-2-cyclopentyl-5-methylpyrimidine.
- 30 27. 6-(1-azepanyl)-N,2-dicyclopropyl-5-nitro-4-pyrimidinamine.

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28. A compound of formula X, or a pharmaceutically acceptable salt thereof.



wherein

5 n is 1-6, and

R¹ is cycloalkyl.

29. A compound of formula X selected from the group consisting of 4-chloro-2-cyclopropyl-6,7-dihydro-5H-pyrido[2,3-d]pyrimidine, 4-chloro-2-cyclopropyl-5,6,7,8-tetrahydro-5H-pyrido[2,3-d]pyrimidine, 4-chloro-2-cyclopropyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepine.
- 10

30. A compound of formula XII, or a pharmaceutically acceptable salt thereof,



15 wherein R¹ is cycloalkyl.

31. 2-cyclopropyl-6,7-dihydro-5H-pyrido[2,3-d]pyrimidin-4-ol.

## Abstract

The present invention concerns chemical compounds combining affinity and antagonism against the human m3 muscarinic receptor with activity as selective phosphodiesterase IV (PDE IV) inhibitors, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals.

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